Anti-Diabetics Drug Usage and Related Pharmaceutical Care Issues among Geriatrics and Non-Geriatrics: A Comparative Assessment

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ABSTRACT

Background and Introduction: Diabetes Mellitus presents a challenge and continues to be a focus of medical care as population continues to age and live longer. The treatment approach in elderly and younger patients is influenced by ageing, life expectancy; co morbidities and severity of the vascular complications which increases the risk for development of pharmaceutical care issues. The present study evaluates anti-diabetic medication use and related pharmaceutical care issues among geriatric and non-geriatric population. **Methods:** A longitudinal cohort study was conducted in patients admitted to tertiary care hospital in north Karnataka with type 2 diabetes mellitus of age 18 years and above. Patient's demographic, clinical characteristics and anti-diabetic medications were reviewed to detect and report any pharmaceutical care issue using Pharmaceutical Care Network Europe checklist. Beers criteria were also utilized for geriatrics assessment. **Results:** A total of 230 diabetic [geriatric 53.48% and non-geriatric 46.52%] patients were finally assessed for the study. Of the total drugs prescribed, anti-diabetic drugs category shared around 25.74% [geriatrics 15.26% and 10.48% in non-geriatrics]. A total of 147 pharmaceutical care issue related to anti diabetics were reported [69.38% in geriatrics and 30.61% in non-geriatrics], which are related to; drug not appropriate for therapy [geriatrics 35.29% non-geriatrics 22.22], Contraindications related [geriatrics 26.47% non geriatrics 17.77%], adverse drug reactions [geriatrics 6.86% non-geriatrics 6.66%] and drug interaction [geriatrics 23.53% non-geriatrics 20%]. **Discussion:** The geriatric population's social factors, thoughts and behavioral patterns, old age and concomitant diseases obscure diabetes management and contribute for the increased frequency of pharmaceutical care issues compare to non-geriatrics. **Conclusion:** The study shows a higher incidence of pharmaceutical care issues in geriatrics compare to non-geriatrics. The treatment plan for diabetes in geriatrics is not dissimilar to that of non-geriatrics. An individualized glycemic goals and interdisciplinary care is the key for optimal management of diabetes in different age groups.

Key words: Geriatric, Non-geriatric, Anti diabetic agents, Pharmaceutical care issues.

INTRODUCTION

The World health organization [WHO] describes Diabetes Mellitus (DM) as a metabolic ailment of multiple causes, distinguished by persistent increase in blood sugar with changes in carbohydrate, fat and protein metabolism which takes place due to disorders with synthesis of insulin, insulin activity, or both. A geographical disparity with unexplained cause was noted distinctly as most of the diabetics in Indian subcontinent are from age group 45-64 years whereas in developed countries the highly diabetic prevalent ages are more than 65 years of age.[1]

DM is a complex, chronic illness which requires continuous medical care with multi-factorial risk reduction strategies beyond glycemic control.[2] The elderly population is rapidly increasing in the world. In India at the year 2000 there were almost 4% of adults suffering from diabetes and it is expected that the incidence rate will increase to 6% in 2025.[3] Although pharmacotherapies gratify 85% of patient's population, lifestyle modification presents itself as a potential source of treatment.[4] In addition, most DM patients are having other health disorders along with it among which the most common are increased blood sugar

and hyperlipidemia. Due to this mostly patients should take numerous medications of about five to nine for maintaining better health and for better outcomes.

The treatment targets are same for younger and old age patients; although treatment plan are taken based on the increase in blood sugar and other risk factors like age, average life time expected, concomitant conditions and rigorousness of the vascular complications.[5,6] The development of diabetic care plan and its management is an exceptional challenge in the geriatric patients with a prerequisite of initial comprehensive assessment and due consideration to pharmacokinetic, pharmacodynamic, and economic aspects.[7]

The main reason of death among diabetes patients is due to cardiovascular disorders i.e. almost 60–80%. The prospective study of diabetes conducted in united-kingdom (UKPDS) says that if the blood sugar levels are controlled as near to normal it can reduce the risk of cardiovascular disorders and other complications in diabetic patients.[8] It has been postulated that metformin might promote Coronary artery disease [CAD][9] and is additionally having the risk of developing lactic acidosis, particularly in patients who have encountered with heart attack recently. The patients with heart related disorders should avoid taking sulphonylureas or glinides and should prefer other treatment options. Renal diseases increase the chances of developing reduced blood sugar levels in diabetes patients. It is because there is reduction in clearance by kidney during renal disease which leads to build up of antidiabetic drugs since there is reduced need of insulin.[9,10] So the recommended drugs to use in case of renal disease with diabetes are glitazones, insulin, glinides or Dipeptidyl peptidase-4 (DPP-4) inhibitors with adjustments in dose.[11]

When a patient is having diabetes with liver disorders like non-alcoholic fatty liver disease (NAFLD) the chances of developing hypoglycemia is high, and the treatment will become difficult because most of the oral antidiabetic drugs are contraindicated and therefore doses must be adjusted in such patients. The diabetes type 2 patients with hepatic disorders are having very high chances of developing cirrhosis of liver, hepatic failure or cancer in liver.[12]

Diabetic patients have higher chances of developing stroke and when compared to non-diabetic population they have double risk for developing stroke. Studies shows that almost 20 % of diabetic patients may die from stroke, which can make it as the main cause of death in diabetic patients.[13] The principal reason for many diabetic patients not achieving the normal blood glucose target is hypoglycemia. If the patient has developed severe hypoglycemia in the past then sufonylureas, glinides and insulin should not be given, and less rigorous blood sugar targets should be kept.[14,15,16] Starting insulin therapy is a very important stage in the management of type 2 DM. Most of the diabetic patients are not able to achieve the target Glycated hemoglobin [A1C] levels by single therapy using oral antidiabetic medications. Type 2 DM has a progressive nature which leads to slow destruction to the β-cell function and its cell mass which eventually leads the patient to the initiation of insulin for the treatment.[17,18] Most of the oral antidiabetic drugs are safe and effective when given in combination with insulin. When metformin is given in combination with insulin there are reduction in side effects like weight gain and hypoglycemia compared with insulin monotherapy. Thiazolidinedione's helps in decreasing insulin resistance but leads to side effects like increased weight, retention of fluid and chances of developing heart failure when given in combination with insulin.[19] The present study evaluates anti diabetics medication usage and related pharmaceutical care issues among geriatric and non-geriatric study population.

METHODS

A longitudinal cohort study was conducted in a tertiary care hospital in north karnataka. Type 2 DM patients of age 18 years and above [≥60 as geriatric and ≤ 60 years as non-geriatrics] with or without concurrent illness were included in the study. Institutional ethics committee has approved the study design. The demographic details of the patient, clinical details, drug therapy, anti diabetic medication prescription were reviewed and assessed for the presence any pharmaceutical care issue. Pharmaceutical Care Network Europe [PCNE] checklist was utilized to assess pharmaceutical care issue with the use of anti-diabetic medication in the both patient population. A Beers criterion was also adopted in geriatrics assessment in addition to PCNE. The data collected was finally computed and reported in percentage using Microsoft word excel sheet 2007.

RESULTS

A total of 230 diabetic patients were included for the study of which geriatric were 123[76(61.78%) male and 47(38.21%) female] and non-geriatric 107 [58(59.79%) male and 39(40.21%) female]. Out of the total geriatric subjects enrolled majority 56.09% were from 60-69 years age and in non-geriatrics 83.05% were of 41-60 years of age. The major co morbidities observed in male and female geriatrics was Cardio vascular system[CVS] disorders [male 56.55% and female 48.6%], followed by

Respiratory disorders, diabetic complications, Central nervous system[CNS], Renal disorders, Gastrointestinal and others etc. Table 1. The major co morbidities observed in male and female non-geriatrics was CVS disorders [male 50% and female 41.3%], followed by diabetic complications, Respiratory disorders, Renal disorders, Gastrointestinal and others etc. Table 1.

Of all the drugs prescribed in the study population, around 25.74% share was of antidiabetic drugs, of which 15.26% [Oral hypoglycemic agents [OHA] 10.98% and 4.28% insulin] in geriatrics with [8.41% as monotherapy and 2.57% as combination] and 10.48% [OHA 5.20% and 5.28% insulin] in non-geriatrics [3.42%as monotherapy and 1.78% as combination]. Majority of insulin as Monotherapy was prescribed in both geriatrics and non-geriatrics patient population Table 2.

A total of 147[102 potential and 45 actual] Pharmaceutical care issues[PCI] related to antidiabetics were reported [126 in geriatrics and 21 in non-geriatrics] in the study population. Of which are related to drug without indication [geriatrics 3.92% non-geriatrics 2.22%] indication without drug [geriatrics 1.96%, non-geriatrics 6.66%] drug not appropriate for therapy [geriatrics 35.29% non-geriatrics 22.22], contraindications[geriatrics 26.47% non geriatrics 17.77%] supratherapeutics dose [geriatrics 0.98% non-geriatrics 2.22%] additive toxicity [geriatrics 2.94% non-geriatrics 2.22%] adverse drug reactions [geriatrics 6.86% non-geriatrics 6.66%], drug interaction [geriatrics 23.53% non-geriatrics 20%] and drug duplication [geriatrics 2.94% non- geriatrics 8.88%] Table 3.

DISCUSSION

The study shows that the percentage of geriatric male patients (61.78%) and non-geriatric male patients (59.79%) diagnosed with type 2 diabetes mellitus was more compared to their female counterparts (38.21%) and (40.21%). Type 2 diabetes mellitus rate was observed to be more in the patients of age 60-70 years in both male (56.09%) and female (65.30%) geriatric patients, whereas in non-geriatric patients type 2 diabetes was more within the age group of 41- 60 years in both male (81.03%) and female (87.17%) patients Table 1.

Table 1: Demographics and clinical characteristics of Geriatrics and Non-geriatrics study population.					
Patient Characteristics					
	Geriatric n=123			**Non geriatric n=107**	
Gender	**Male[%]**	**Female [%]**		**Male [%]**	**Female [%]**
	76[61.78]	47[38.21]		64[59.79]	43[40.21]
Mean sd±	68.91±7.35	68.72±7.39		49.73±8.11	49±9.08
Age group	**Geriatrics**			**Non Geriatrics**	
distribution	**Male [%] n=76**	**Female [%] n=47**		**Male [%] n=64**	**Female [%] n=43**
60-70	41[53.95]	29[61.70]	18-20	1[1.57]	--
71-80	20[26.32]	16[34.04]	21-40	11[17.19]	6[13.96]
81-90	15[19.74]	2[4.26]	41-59	52[81.25]	37[86.05]
Associated	**Geriatrics**			**Non Geriatrics**	
Co-morbidities	**Male [%] n=76**	**Female [%] n=47**		**Male [%] n=64**	**Female [%] n=43**
CVS	69[56.55]	36[48.6]		41[50]	24[41.3]
Diabetes complication	14[11.47]	15[20.2]		14[17.07]	15[25.86]
CNS	07[5.73]	11[14.86]		05[6.09]	----
Respiratory disorders	18[14.75]	05[6.7]		04[4.87]	08[13.79]
Renal disorders	04[3.27]	03[4.05]		03[3.65%]	01[1.72]
Gastrointestinal disorders	02 [1.63]	02[2.70]		06[7.31%]	01[1.72]
Anemia	04[3.27]	02[2.70]		---	-----
others	04[3.27]	----		09[10.97]	09[15.51]

CVS; Cardiovascular system disorders, CNS; Central nervous system disorders

Table 2: Pattern of Oral Hypoglycemic Agents and Insulin used in Geriatrics and Non-geriatrics population.

OHA	Geriatric n=214	Non-geriatric n=147
Monotherapy	**n=118**	**n=48**
Metformin	53[44.91%]	31[64.5%]
Gliclazide	09[7.62%]	06[12.5%]
Voglibose	08[6.77%]	03[6.25%]
Glimepiride	06[5.08%]	03[6.25%]
Glipizide	06[5.08%]	----
Pioglitazone	----	04[8.33%]
Repaglinide	**----**	01[2.08%]
Combination	**n=36**	**n=25**
Glimipride + metformin	15[41.66%]	07[28%]
Glipizide + Metformin	12[33.33%]	03[12%]
Voglibose + Metformin	03[8.33%]	----
Pioglitazone + Metformin	02[5.55%]	01[4%]
Gliclazide + metformin	01[2.77s%]	01[4%]
Glibenclamide + metformin	----	09[36%]
Nateglinide + metformin	-----	01[4%]
Glimepride+pioglitazone+Metformin	03[8.33%]	03[12%]
Insulin	**n=60**	**n=74**
Monotherapy		
Actrapid	38[63.33%]	35[47.29%]
Recosulin	09[15%]	21[28.37%]
Basalog	04[6.66%]	----
Lupisulin	04[6.66%]	01[1.35%]
Insugen	01[1.66%]	06[8.10%]
Huminsulin	----	04[5.40%]
Combination		
Mixtard	04[6.66%]	07[9.45%]

Table 3: Pharmaceutical Care Issues identified in Geriatrics and Non-Geriatrics study population.

Pharmaceutical care issues category	Pharmaceutical Care Issues n=147					
	Geriatrics n=102			Non-Geriatrics n=45		
	Male	Female	%	Male	Female	%
Drug without indication	3	1	3.92	1	0	2.22
Indication without drug	1	1	1.96	2	1	6.66
Drug not appropriate for therapy	21	10	30.39	9	6	33.33
Contraindications	18	9	26.47	5	3	17.77
Supratherapeutic dose	1	0	0.98	0	1	2.22
Additive toxicity	3	0	2.94	1	0	2.22
Suspected ADR's	2	5	6.87	3	0	6.66
Drug - Drug interaction	14	10	23.53	3	6	20
Drug Duplication	2	1	2.94	2	2	8.88
Total PCI	**65**	**37**	**100%**	**26**	**19**	**100%**

PCI; Pharmaceutical Care Issues

The most common co-morbid condition associated with type 2 DM in both gender geriatric patients and non-geriatric patients was found to be CVS disorders [56.55% ,48.6% and 50%, 41.3%] Followed by diabetic induced complications, respiratory and, renal disorders etc. Table 1.

The study observed most commonly used OHA monotherapy agent was metformin (44.91%), followed by sulfonylurea (17.78%) and in combination therapy was Metformin with Glimepiride (41.66%) in geriatrics, which was also observed in non-geriatrics with monotherapy of metformin (64.5%), followed by sulfonylureas (18.75%) and combination therapy was Metformin with Glimepiride (286%).This indicates that metformin and glimepride+ metformin was the choice of drug in both geriatrics and adults. But the usage of metformin was more in adult population. Human Actrapid was found to be the most commonly used insulin for type 2 diabetes mellitus therapy among both geriatric (63.3%) and non-geriatric (47.29%) patients. Table 2.

The study observed a total of 147 different pharmaceutical care issues [PCI] in both geriatrics [69.39%] and non-geriatrics [30.61%]. Frequency of PCI was higher in geriatrics subjects compare to non-geriatrics; the probable reason could be, ageing characteristics of the subjects, co-morbidities and multiple medication use, which increases the risk of development of PCI. It has been postulated that metformin might promote CAD and can also have an increased chance of leading to development of lactic acidosis mostly in patients encountered with heart attack recently.[9] In cardiac muscle cells and smooth muscle cells in arteries, Adenosine triphosphate - sensitive potassium channel [K_{ATP} channels] are seen abundantly. Sulfonylurea's increases the secretion of insulin by binding to the K_{ATP} channels in pancreatic β-cell; therefore, there are many chances that these drugs can bind to K_{ATP} channels in cardiac muscle cells and vascular smooth muscle cells. In cardiac muscle cells the K_{ATP} channels intercede for preconditioning of ischemia. The exposure of cardiac muscle cells to various episodes of ischemia can induce changes in cell adaptations thus making these cells resistant to injuries during consequent ischemic attacks[6]. There were 19 geriatrics and 7 non-geriatric cases were identified in which sulfonylureas were used in CAD. Table 3.

Sulfonylureas are generally not to be recommended in renal impairment. Because during kidney diseases there will be Prolonged half-life with reduced renal excretion of Sulfonyl urea which has been shown to increase the incidence of reduced blood sugar level complexities (hypoglycemia) to about five times more than in patients

without kidney disease.[9] In this study a case of geriatric patient in which sulfonylureas (glipizide) was used in renal impairment was observed Table 3.

The use and contraindications of antidiabetic drugs during cerebrovascular disease matches generally with cardiovascular disease recommendations.[8] During cerebro vascular disease all the antidiabetic drugs except sulphonylureas and glinides can be used for the diabetic therapy. A few geriatric cases were identified where Sulfonylureas were used in stroke Table 3. Nicotinamide Adenine Dinucleotide [NAD+] required to convert lactate to pyruvate is supplied during gluconeogenesis. The antidiabetic drugs from biguanide class inhibit gluconeogenesis in the liver and kidney which increases the chance of development of lactic acidosis if the liver functions are impaired. Metformin induced hepatotoxicity cases are only a few but because of chances of development of lactic acidosis with metformin use in liver impaired patients, metformin is contraindicated in advanced hepatic disorder patients. A geriatric and a non-geriatric case were identified where metformin was used in liver impairment Table 3. Since Sulfonylureas are not expensive drugs and are well tolerated by patients, it is commonly used antidiabetic drug and it is among the first oral antidiabetic drugs developed. They usually act by stimulating the synthesis of insulin from pancreas and thus show its anti-diabetic effect.[13] A few (4) geriatric cases were identified where sulfonylureas were used in hypoglycemia Table 3. The study reveals around 15.21% of total OHA prescribed in both geriatrics and non-geriatrics were inappropriate in terms of drug selection, dosage regimen, patient preferences and against established practice of therapy owing to possible physician preference, evidence based or peer practice. The study reveals that there was a wide usage of insulin and sulfonylureas among the geriatrics which was generally considered to be unsafe, because both the treatments ultimately lead to severe hypoglycemia. 67 geriatric cases were identified for inappropriateness in therapy, among which 25 cases had inappropriateness in insulin prescription where insulin was prescribed with Fasting blood glucose [FBG] ≤ 250 mg/dl and 42 cases had inappropriateness in prescription of sulfonylurea Table 3. It was reasonable approach to initiate treatment with oral agents in most of the patients, with an exemption for the patients with severe hyperglycemia (Plasma glucose in empty stomach > 250 mg/dl). Such patients need insulin therapy, or basal bolus insulin treatment to reduce blood sugar levels. In other case starting oral treatment can be very much successful[14] Table 3.

The study also observed episodes of adverse drug effect with use of antidiabetic, with majority in geriatric females

(5 episodes), followed by geriatric males (2 episodes) and male non-geriatrics (3 episodes) with events ranging from hypoglycemia [insulin, glimepride] to metallic taste [metformin]. The study reveals potential drug interaction in the study population. The geriatrics was observed with higher number (24) of drug interaction compare to non-geriatrics (9). The interaction observed was of mild to moderate in nature, but the risk was higher in geriatrics patients due to poly pharmacy or increased number of drug use Table 3.

CONCLUSION

The study reveals similar pattern of disease management in older and younger diabetic patients using antidiabetic drugs with some exemption. Advance age, nutrition, behavioral and social factors, and other concomitant medical conditions promotes the complexity of diabetes management in elderly when compared to the younger patients influencing increased risk for the precipitation of drug related problems and pharmaceutical care issues. The key for optimal management of diabetes should involve a comprehensive assessment of diabetic patient to bring about individualized drug therapy in the context of ageing phenomenon, complexity of diseases and concurrent illness to ensure safe and effective treatment outcome.

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CONFLICT OF INTEREST

No conflict of interest.

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