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Comparison of the Quality of Life of Type 2 Diabetes Mellitus Patients Treated with Biguanides, Thiazolidinediones and Sulphonyl ureas

Vishvas Garg*

Ph.D student, University of New Mexico, College of Pharmacy, Dept of Pharmacy Practice, 212 Princeton Dr.SE, Apt # B, Albequrque, NM-87106, USA.

ABSTRACT

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Currently, more than 250 million people are suffering from diabetes mellitus (DM) worldwide. The purpose of this paper was to determine and compare the impact of the drug induced adverse drug reactions (ADRs) caused by biguanides, thiazolidinediones and sulfonylureas on the Health-Related-Quality-of-Life (HRQoL) in the T2DM patients. Using PubMed MeSH terms, comprehensive drug induced ADRs profiles of biguanides, thiazolidinediones and sulfonylureas were developed, separately. Furthermore, health utility values associated with each of the ADRs were determined using literature search. Quality-Adjusted-Life-Years (QALY's) measure was used to calculate and compare the impact of drug induced ADRs on HRQoL of the patients. Overall, we found that, followed by sulfonylureas and thiazolidinediones, metformin induced ADRs cause maximum decrement in the HRQoL of T2DM patients. We further found existence of both between group and within drug group differences between the magnitudes of the impact of different drug induced ADRs on the HRQoL of patients.

Keywords: Biguanides, Thiazolidinediones, Sulfonylureas, quality of life, adverse drug reactions, type 2 diabetes mellitus, quality-adjusted-life-years

INTRODUCTION AND BACKGROUND

Currently, in India, 50.8 million people are suffering from diabetes mellitus (DM).[1] By the end of the year 2030, including in India, the global prevalence of DM is expected to increase by 151%, i.e. from 171 million persons in 2000 to 336 million people in 2030.[2] This substantial increase can be largely attributed to factors such as the population growth and ageing, increased obesity and physical inactivity, and increased lifeexpectancy of people with diabetes.[3-5] Additionally, the World Health Organization (WHO) estimates that, in India, between the years 2006 and 2015, the total loss of national income from DM will be 336.6 billion International Dollars.[6]

Diabetes Mellitus is of three main types: type 1 DM (insulin-dependent diabetes), type 2 DM (non-insulin dependent diabetes), and gestational diabetes mellitus.[7] About 90-95% of all the DM patients are of the type 2 diabetes mellitus (T2DM).[7] It is a progressive disorder with an insidious onset.

The most common precipitating cause of T2DM is the beta-cell dysfunction.[8] The other metabolic disorders associated with T2DM are: chronic hyperglycemia, hepatic glucose production in the prandial state, and insulin insensitivity in fat and muscle cells.[9,11] The common risk factors of T2DM are: impaired glucose intolerance, age over 45 years, family history of diabetes, polycystic ovarian syndrome, high blood pressure, obesity, physical inactivity, low high-density lipids or high triglycerides levels, being of certain racial and ethnic groups, and women who had gestational diabetes.[12,13] Furthermore, T2DM can lead to several macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy).[14,15]

A range of classes of oral therapeutic agents exists for the treatment of T2DM, including biguanides, sulfonylureas, and thiazolidinediones. Numerous clinical trials have demonstrated that biguanides, thiazolidinediones and sulfonylureas increase the health related quality of life (HRQoL) of the T2DM patients. However, each of these therapies causes several adverse drug reactions (ADRs). These ADRs reduces HRQoL of the patients. Nonetheless, the ADRs associated with each of these drugs are of different types and occur at different rates.Therefore, in order to understand the effect of each ADRs on the HRQoL of the T2DM patients, the purpose of this paper is to determine and compare the impact of the ADRs on the HRQoL in the T2DM patients, caused by biguanides, thiazolidinediones and sulfonylureas.

Address for Correspondence:

Vishvas Garg, Ph.D student, University of New Mexico, College of Pharmacy, Dept of Pharmacy Practice, 212 Princeton Dr.SE, Apt # B, Albequrque, NM-87106, USA.

E-mail: vishvas4588@gmail.com

MATERIALS AND METHODS

Literature Review:

The types and rates of ADRs caused by biguanides, thiazolidinediones, and sulfonylureas were determined using the published literature. Separately, comprehensive profiles of drug induced ADRs were developed for biguanides, thiazolidinediones, and sulfonylureas. For this purpose, using the Boolean indicators "AND" and/or "NOT" in separate searches, PubMed was searched for the following MeSH terms: biguanides, metformin, thiazolidinediones, rosiglitazone, pioglitazone, sulfonylureas, glyburide, and glibenclamide. Only randomized clinical trials in English language were included. All the references cited in the above retrieved articles were also reviewed for relevance and their full-text was obtained when applicable.

Determination of Impact of ADRs on Quality of Life:

The impact of ADRs on patients HRQoL was determined using the Quality-Adjusted-Life-Year's (QALY's) measure.[16] It takes into account both the quantity and quality of life generated by any healthcare intervention. One healthcare intervention might help to increase the lifespan, nonetheless, it might also have serious adverse effects. Whereas, another healthcare intervention might not be as effective as the first one in increasing the life-span, but it might have lesser adverse effects caused by it and can therefore provide better HRQoL while the patients are alive.

While calculating QALY's, the amount of time spend in a health state is weighted by the utility score given to that health state. The utility scores can vary from 0 to 1, with 0 being worst possible health state or death and 1 being perfect health. To gain one full QALY, it takes on year of perfect health. Thus, an intervention that generates ten additional years in a health state valued at 0.50 will generate 5 QALY's.

Using QALY's, to measure the impact of ADRs on the HRQoL of T2DM patients, the rates of incidences of each of the ADRs were multiplied by 100,000 to determine the incidence of ADRs per 100,000 persons. Separately, the values of these incidences were multiplied by the respective health utility weights associated with that condition to determine the QALY's gained in that particular health condition per 100,000 persons in one year. The QALY's gained in that health condition were then subtracted from 100,000 which is the QALY's gained by 100,000 persons in one year of perfect health. The values obtained are QALY's lost due to that particular ADRs per 100,000 persons in one year. These QALY's lost per 100,000 persons in one year due to any ADR shows the impact of ADRs on the HRQoL of T2DM patients.

RESULTS AND DISCUSSION

We found several ADRs caused by biguanides, sulfonylureas, and thiazolidinediones. Based on the review, we divided these ADRs into four main categories: body as a whole events, digestive system events, cardiovascular events, and all other events (Table 2). Some ADRs, such as headache, musculoskeletal pain, and upper respiratory tract infection were common across all the drugs. On the other hand, other ADRs were limited to either one or two drug classes. For instance, hyperglycemia was limited to thiazolidinediones and cardiovascular deaths were limited to sulfonylureas and thiazolidinediones classes of drugs. Furthermore, all the ADRs were found to have different incidence rates for biguanides, sulfonylureas, and thiazolidinediones (Table 1).

Additionally, each drug induced ADR was found to have different health utilities decrements caused by them in T2DM patients (Table 2), some higher others not. For example, infections caused substantial lowering of the quality-of-life (health utility decrement=0.05(17)), whereas weight gain/loss did not had much impact on the quality-of-life of the patients (health utility decrement =0.910.[18]

Table 2: Qaly Decrements Caused by the ADRs

Health States	Health Utility weights
Body as a whole	
Accidental Injury	0.52(29)
Headache	0.77(30)
Infection	0.05(17)
Musculoskeletal/Back pain	0.70(31)
Fatigue	0.75(30)
Anemia	0.56(32)
Edema	0.99(33)
Fracture	0.34(34)
Digestive system Events	
Diarrhea	0.32(35)
Dyspepsia/Indigestion	0.54(36)
Nausea/vomiting	0.32(35)
Flatulence	0.82(37)
Abdominal Discomfort	0.82(37)
Cardiovascular Events	
Myocardial Infarction	0.64(38)
Stroke	0.50(39)
Cardiovascular deaths	0.50(40)
Other Events	
Weight gain/loss	0.91(18)
Hypoglycemia	0.55(41)
Upper Respiratory Tract infections	0.63(42)
Hyperglycemia	0.55(41)

Table 1. Incidences of ADRS from Different Therapies.

Adverse Drug Reactions	Metformin	Glyburide	Thiazolidinediones
Body as a whole			
Accidental Injury	7.3%(19)	-	7.6%(22)
Headache	4.9%(23)	8.5%(24)	10%(21)
Infection	20.5%(19)	-	5.0%(22)
Musculoskeletal/Back pain	7.2%(24)	9.8%(24)	5.5%(25)
Fatigue	5.9%(24)	5.5%(24)	3.6%(22)
Anemia	2.2%(19)	0.6%(20)	1.9%(22)
Edema	2.2%(19)	1.0%(20)	26.7%(25)
Fracture	5.1%(19)	3.5%(20)	9.3%(22)
Digestive System Events			
Diarrhea	24.8%(24)	6.1%(24)	7%(21)
Dyspepsia	7.1%(19)	4%(20)	9%(21)
Nausea/vomiting	10.4%(23)	6.6%(23)	8%(21)
Flatulence	12.1%(19)	2%(20)	-
Abdominal Discomfort	6.4%(19)	4%(23)	0.3%(26)
Cardiovascular			
Events Myocardial Infarction	-	-	8.1%(25)
Stroke	-	-	2.9%(25)
Cardiovascular deaths	-	2.3%(25)	1.9%(25)
Other Events			
Weight gain/loss	3.4%(19)	4.9%(27)	2.6%(25)
Upper Respiratory Tract infections	16.3%(28)	17.6%(28)	4.3%(22)
Hyperglycemia	-	-	3.9%(22)
Hypoglycemia	3.4%(22)	43.4%(27)	9.8%(26)

Overall, the ADRs caused by the administration of Metformin to the T2DM patients were found to have highest total decrease in HRQoL of these patients (i.e. metformin induced ADRs caused loss of 69,312 QALY's per 100,000 persons in one year) followed by thiazolidinediones (i.e. loss of 47,124 QALY's per 100,000 persons in one year) and glyburide (i.e. loss of 46,982 QALY's per 100,000 persons in one year). The details are displayed in Table 3.

In addition, each drug induced ADR impacted HRQoL differently among the three drug groups, i.e. biguanides, sulfonylureas, and thiazolidinediones. For example, the decrease in HRQoL of patients was highest due to upper respiratory tract infections induced by glyburide (i.e. loss of 6,348 QALY's per 100,000 persons in one year) followed by metformin (i.e. loss of 5,880 QALY's per 100,000 persons in one year) and thiazolidinediones (i.e. loss of 1,551 QALY's per 100,000 persons in one year).

Furthermore, we found within group differences on the impact of ADRs on HRQoL of patients within drug group. For example, incomparison to metformin induced anemia, metformin induced diarrhea caused significantly higher reduction in the HRQoL of patients, i.e. loss of 950 and 19,309 QALY's per 100,000 persons in one year, respectively.

The primary reasons for the differences in the impacts on the HRQoL due to different drugs were the differences among the ADRs incidence rates between drugs and differences in health utilities decrements due to each ADR (Table 2). For example, due to difference in rates of dyspepsia between the three drugs (i.e. metformin, glyburide, and thiazolidinediones causing dyspepsia with rates 7.1%,[19] 4%,[20] and 9%,[21] respectively), the impact on the HRQoL of patients was different, i.e. 3205, 1805, and 4062 QALY's lost per 100,000 persons in one year due to biguanides, sulfonylureas, and thiazolidinediones, respectively.

Overall, we found that, when administered, metformin induced ADRs cause maximum decrement in the HRQoL of T2DM patients. We further found existence of both between group and within drug group differences between the magnitudes of the impact of different drug ADRs on the HRQoL of patients. Nonetheless, this study has several

*TABLE 3. QALY's Gained and Lost due to Different Drugs and ADRs.

	Metformin			Glyburide			Thiazolidinediones		
Adverse Drug Reactions	**QALY's gained in ADR**	**Possible QALY's when no ADR occur**	**QALY's Lost due to ADR**	**QALY's gained in ADR**	**Possible QALY's when no ADR occur**	**QALY's Lost due to ADR**	**QALY's gained in ADR**	**Possible QALY's when no ADR occur**	**QALY's Lost due to ADR**
QALY'sBody as a whole Accidental									
Injury	3853	7300	3447	-	-	-	4012	7600	3588
Headache	3812	4900	1088	6613	8500	1887	7780	10000	2220
Infection	1191	20500	19309	-	-	-	291	5000	4710
Musculoskeletal/Back pain	5099	7200	2101	6940	9800	2860	3895	5500	1605
Fatigue	4472	5900	1428	4169	5500	1331	2729	3600	871
Anemia	1250	2200	950	341	600	259	1080	1900	820
Edema	2196	2200	4	998	1000	2	26657	26700	43
Fracture	1777	5100	3323	1220	3500	2280	3241	9300	6059
Digestive System Events									
Diarrhea	8149	24800	16651	2004	6100	4096	2300	7000	4700
Dyspepsia	3895	7100	3205	2195	4000	1805	4938	9000	4062
Nausea/vomiting	3417	10400	6983	2169	6600	4431	2629	8000	5371
Flatulence	10028	12100	2072	1658	2000	342	-	-	-
Abdominal Discomfort	5304	6400	1096	3315	4000	685	249	300	51
Cardiovascular Events									
Myocardial Infarction	-	-	-	-	-	-	5256	8100	2844
Stroke	-	-	-	-	-	-	1453	2900	1447
Cardiovascular deaths	-	-	-	1171	2300	1129	967	1900	933
Other Events									
Weight gain/loss	3124	3400	276	4504	4900	396	2390	2600	210
Upper Respiratory Tract infections	10420	16300	5880	11252	17600	6348	2749	4300	1551
Hyperglycemia	-	-	-	-	-	-	2181	3900	1719
Hypoglycemia	1901	3400	1499	24269	43400	19131	5480	9800	4320
TOTAL	**69888**	**139200**	**69312**	**72818**	**119800**	**46982**	**80277**	**127400**	**47124**

=*All QALY ' s gained or lost are per 100,000 persons in one year

limitations. First, in our results, we did not include the improvements in the HRQoL of patients due to administration of biguanides, thiazolidinediones, or sulfonylureas. The primary reason for this is that the purpose of our study was to determine the impact of drug induced ADRs on the HRQoL of patients, not to determine the overall impact on the HRQoL. Second, our study is limited to biguanides, thiazolidinediones, and sulfonylureas. In our analysis, we did not include other T2DM therapeutic agents such as, diphenyl peptidyl-4 (DPP-4) inhibitors, glucagon like peptides-1 analogues, and acarbose. Third, the results of this study are based on published literature review, not primary data. These studies were conducted in different settings, like in different countries and on different populations, and, therefore, pooling of results of such studies can lead to uncertainty in the results.

CONCLUSION

We compared the impact of biguanides, thiazolidinediones, or sulfonylureas induced ADRs on the HRQoL of T2DM patients. We conducted a systematic literature review and developed the drug induced ADRs profiles of biguanides, thiazolidinediones, and sulfonylureas. We further determined the health utility decrements caused by these ADRs. Furthermore, the results of this study show that metformin induced ADRs cause maximum reduction in the HRQoL of T2DM patients. This was found to be followed by thaizolidinediones, and glyburide induced ADRs.We further found both between group and within group differences in the impact of drug induced ADRs on the HRQoL of T2DM patients for biguanides, sulfonylureas, and thiazolidinediones.

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