Original Article

Study of Prevalence and Effects of Multiple Drug Intake in Elderly Type 2 Diabetes Patients with Associated Comorbidities

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Abstract

Background: Elderly patients with diabetes are a vulnerable group especially for associated co-morbidities. The physicians should be aware of the pitfalls of caring for these patients and prioritize an individualized treatment plan to ensure an optimal glycemic control, without placing the patient at unnecessary risk. **Objective:** Assess the effects of multiple drug intakes in elderly type 2 diabetes patients with associated comorbidities. **Patients & Methods**: This study included 100 patients with type 2 diabetes and other associated comorbidities recruited from the outpatient clinic of Internal Medicine Department, Alexandria Main University Hospital. The studied patients were divided in to two groups: Group I**;** 50 patients aged 55-64 years and group II: 50 patients ≥65 years. Each group was further re-divided to (A) subdivision: patients who were receiving <5drugs and (B) subdivision: pients who were receiving ≥5 drugs. The effects of polypharmacy in elderly type 2 diabetes patients with comorbidities especially on drug adherence and the observed adverse drug events were assessed. **Results:** Our results demonstrated that non adherence to drugs was significantly higher in patients who received ≥5 drugs in group I compared to those who received <5 drugs. In comparison between the polymedicated groups (IB and IIB), non adherence was significantly higher in IIB group. Among the studied adverse drug events, arrhythmia, repeated hypoglycemia, orthostatic hypotension, GIT upsets and bleeding events were significantly higher in group (IIB) than group (IB). **Conclusion:** Prescription in elderly diabetics must balance between the need for drugs and hazards of polypharmacy. Medication non-adherence and adverse drug events are major consequences of polypharmacy.

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Key Words: Polypharmacy, Type 2 DM, Elderly population.

INTRODUCTION

Recent advances in pharmacological therapy, although offer hope for patients, its inappropriate use carry some risks. [1] Prescription for the elderly is particularly challenging owing to the high prevalence of comorbidities in these population. [2] In general, polypharmacy means the use of multiple drugs without clear cutoff point. [3] A more practical definition for polypharmacy entails the use of multiple drugs that are not obviously needed. [4]

Diabetes is a highly prevalent systemic disease with lots of complications including microvascular complications (retinopathy, nephropathy, neuropathy and dermopathy) and macrovascular ones (cerebrovascular diseases, peripheral vascular diseases and coronary heart diseases).[5] Many comorbid conditions are frequently encountered in elderly patients with diabetes like hypertension and

dyslipidemia in addition to the high incidence of geriatric syndromes like fall, depression and cognitive dysfunction. [6] That's why management of diabetes with its complications and associated comorbidities make these patients prone to hazards of polypharmacy.

PATIENTS & METHODS

This study included 100 patients with type 2 diabetes associated with other comorbidities recruited from the Outpatient Clinic of the Department of Internal Medicine of the Main University Hospital of Alexandria during the period of 2017-2018. The patients were classified into 2 groups each of 50 patients; group I included patients aged between 55 and 64 years and group II included patients aged ≥65 years. Each group was further subdivided in relation to total number of drug intake in to (A) subdivision including patients receiving <5 drugs and (B) subdivision including patients receiving ≥5 drugs (polymedicated).

The study protocol was approved by the Ethics Committee of Alexandria University. The study was conducted according to the criteria set by the Declaration of Helsinki and each subject signed an informed consent before participating in the study.

All cases were subjected to complete history taking with emphasis on drug history. Data were obtained about the presence of new symptoms due to drug intake with differentiation whether they were adverse drug events or drug-drug interaction. An Adverse Drug Event (ADE) is defined as 'any physical or mental harm resulting from medication use be it misuse, under-dosing or overdosing' [11]. A drug interaction is defined either as increase or decrease of a medical diagnostic or therapeutic effect of a specific drug caused by another substance, which may be another drug, plant or a dietary supplement [12]. Full clinical examination was done to all included patients. In addition, glycated hemoglobin (HbA1C %) was done to assess glycemic control.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS 21.0, IBM/SPSS Inc., Chicago, IL) software. Baseline characteristics of the study population were presented as frequencies and percentages (%) or mean values and standard deviations (SD) and median and range (after testing of normality by Kolmogorov-Smirnov and Shapiro-Wilk's tests).

For comparison of data, Chi-Square test (or Fisher's exact test) was used to compare two independent groups of qualitative data. For quantitative data, independent-Samples t-test and Mann-Whitney U test were used to compare two groups of parametric and non-parametric quantitative data respectively. For all tests, P values <0.05 are considered significant.

RESULTS:

Table I shows the baseline characteristics of the studied population. There was no significant difference in terms of male/female ratio. Body mass index (BMI) was significantly higher in group I. The mean diabetes duration was 7.04 ± 4.97 and 12.14 ±6.53 in group I and II respectively.

Table I: Comparison between the two studied groups according to demographic data

	Total (n=100)		Age (years)				Test of Sig.	P
			Group I (n = 50)		Group II (n = 50)			
	No.	%	No.	%	No.	%		
Sex								
Male	52	52.0	28	56.0	24	48.0	χ^2= 0.641	0.423
Female	48	48.0	22	44.0	26	52.0		
BMI (kg/m^2)								
Min. – Max.	23.0 –36.0		26.0 –34.0		23.0 –36.0		t= 2.315*	0.023*
Mean ± SD.	29.80 ±2.21		30.30 ±1.92		29.30 ±2.38			
Median (IQR)	30.0 (28.0 –31.0)		30.0 (29.0 – 32.0)		29.0 (32.0 – 31.0)			
Diabetes duration								
Min. – Max.	1.0 –31.0		1.0 –25.0		31.0		U= 642.0*	<0.001*
Mean ± SD.	9.59 ±6.32		7.04 ±4.97		12.14 ±6.53			
Median (IQR)	9.0 (4.0 –14.0)		7.0 (3.0 – 10.0)		12.50 (7.0 – 15.0)			

χ^2: **Chi square test** **t: Student t-test**
p: p value for comparing between the studied groups
*: Statistically significant at p ≤ 0.05

The detected comorbidities in the included patients were: hypertension (HTN), dyslipidemia, arthropathies, gout, ischemic heart disease (IHD), stroke, cognitive problems, urinary incontinence and hepatitis C virus (HCV). Among them, arthropathies, IHD and stroke were significantly higher in group II (p=0.003, p=<0.001, p=0.006) respectively.

As shown in table II 80% of the studied population were receiveing ≥5 drugs. The number of patients who were receiving ≥5 drugs (polymedicated patients) were significantly higher in group II.

Table II: Comparison between the two studied groups according to total number of drugs

Total number of drugs	Total (n=100)		Age (years)				Test of sig.	P
			Group I (n = 50)		Group II (n = 50)			
	No.	%	No.	%	No.	%		
<5 (A)	20	20.0	16	32.0	4	8.0	χ^2=9.0*	0.003*
≥5 (polymedicated (B))	80	80.0	34	68.0	46	92.0		
Min. – Max.	3.0–14.0		4.0–14.0		3.0–13.0		U= 749.0*	<0.001*
Mean ± SD.	6.98±2.58		6.18±2.46		7.78±2.47			
Median (IQR)	7.0(5.0–9.0)		5.0(4.0–8.0)		7.0(6.0–10.0)			

U: Mann Whitney test
p: p value for comparing between the studied groups
*: Statistically significant at p ≤ 0.05

The relation between the total number of drugs and drug adherence is demonstrated in Table III. Non adherence to drugs was significantly higher in patients who received ≥5 drugs in group I compared to those who received <5 drugs. In comparison between the polymedicated groups (IB and IIB), non-adherence was significantly higher in IIB group.

Table III: Relation between total number of drugs and adherence

	Total number of drugs							
	Group I (n = 50)				**Group II (n = 50)**			
	<5 (IA) (n = 16)		**≥5 (1B) (n = 34)**		**<5(IIA) (n = 4)**		**≥5 (IIB) (n = 46)**	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Adherence								
Yes	16	100.0	15	44.1	2	50.0	8	17.4
Non adherence	0	0.0	19	55.9	2	50.0	38	82.6
$\chi^2(p_1)$	14.421*(<0.001*)				2.446 (^{FE}p=0.174)			
$\chi^2(p_2)$	6.817* (0.009*)							

χ^2: **Chi square test**, FE**: Fisher Exact**
p_1: p value for comparing between <5 and ≥ 5 in each group
p_2: p value for comparing between group I and II for ≥5 group
*: Statistically significant at $p \leq 0.05$

Regarding the adverse drug events there was significant difference in the incidence of arrhythmia, repeated hypoglycemia, orthostatic hypotension, gastrointestinal (GIT) upsets and bleeding tendency between the patients in the two studied groups being higher in the older patients (group II) (p= 0.007, 0.012, 0.007, 0.001, 0.008) respectively. Other adverse events did not reveal significant difference between the two groups. Table (IV) shows the relation between the total number of drugs and the detected drug adverse events in the studied groups. Arrhythmia, repeated hypoglycemia, orthostatic hypotension, GIT upsets and bleeding events were significantly higher in elderly polymedicated group (IIB) than polymedicated patients less than 65 year old (IB) group.

Table IV: Relation between total number of drugs and adverse drug events

Adverse drug effect	Total number of drugs							
	Group I (n = 50)				Group II (n = 50)			
	<5 (IA) (n = 16)		≥5 (IB) (n = 34)		<5 (IIA) (n = 4)		≥5 (IIB) (n = 46)	
	No.	%	No.	%	No.	%	No.	%
Arrhythmia	0	0.0	2	5.9	0	0.0	11	23.9
$\chi^2(p_1)$	0.980 (^{FE}p=1.000)				1.226 (^{FE}p=0.563)			
$\chi^2(p_2)$	4.670*(0.031*)							
Repeated hypoglycemia	0	0.0	0	0.0	0	0.0	7	15.2
$\chi^2(p_1)$	-				0.708 (^{FE}p=1.000)			
$\chi^2(p_2)$	5.670*(^{FE}p=0.019*)							
Orthostatic Hypotension	0	0.0	2	5.9	0	0.0	11	23.9
$\chi^2(p_1)$	0.980 (1.000)				1.226 (^{FE}p=0.563)			
$\chi^2(p_2)$	4.670*(0.031*)							
GIT upsets	6	37.5	13	38.2	2	50.0	34	73.9
$\chi^2(p_1)$	0.002 (0.960)				1.044 (0.310)			
$\chi^2(p_2)$	10.269*(0.001*)							
Bleeding tendency	0	0.0	1	2.9	0	0.0	9	19.6
$\chi^2(p_1)$	0.480 (^{FE}p=1.000)				0.954 (1.000)			
$\chi^2(p_2)$	4.940*(0.038*)							
Hyperuricemia	0	0.0	4	11.8	0	0.0	4	8.7
$\chi^2(p_1)$	2.046 (^{FE}p=0.292)				0.378 (^{FE}p=1.000)			
$\chi^2(p_2)$	0.205(^{FE}p=0.717)							
Dry cough	0	0.0	0	0.0	0	0.0	4	8.7
$\chi^2(p_1)$	-				0.378 (^{FE}p=1.000)			
$\chi^2(p_2)$	3.112 (^{FE}p=0.133)							
Lower limb edema	0	0.0	0	0.0	0	0.0	5	10.9
$\chi^2(p_1)$	-				0.483(^{FE}p=1.000)			
$\chi^2(p_2)$	3.942(^{FE}p=0.069)							
Dry mouth	0	0.0	0	0.0	0	0.0	1	2.2
$\chi^2(p_1)$	-				0.089 (^{FE}p=1.000)			
$\chi^2(p_2)$	0.784 (^{FE}p=1.000)							
Headache	0	0.0	6	17.6	0	0.0	4	8.7
$\chi^2(p_1)$	3.209 (^{FE}p=0.159)				0.378(^{FE}p=1.000)			
$\chi^2(p_2)$	1.432(^{FE}p=0.310)							

χ^2: **Chi square test**, FE**: Fisher Exact**
p_1: p value for comparing between <5 and ≥ 5 in each group
p_2: p value for comparing between group I and II for ≥5 group
*: Statistically significant at p ≤ 0.05

Regarding glycemic control, the mean glycated hemoglobin (HbA1c) were significantly higher in IB (8.26 ± 0.83) than IA subdivision (7.46 ± 0.55) of group I (P=0.001), while there was no significant difference between IIA and IIB subdivisions. On comparing the polymedicated subdivisions (IB, IIB) in both groups, no significant difference was detected regarding the mean HbA1c (p=0.290).

DISCUSSION:

Diabetes Mellitus (DM) is an important health issue for the elderly population. [7] More than half of patients with diabetes mellitus have two or more associated diseases.[8,9] Multimorbidity, commonly characterized as the co-existence of two or more chronic health conditions, is common within the elderly.[10] Polypharmacy is defined as "the administration of many drugs at the same time or the administration of an excessive number of drugs".[11] But unfortunately, there's no standard cut point with respect to the number of drugs that's

agreed upon for the definition. The foremost commonly utilized term was polypharmacy which was characterized as five or more drugs. [12] Comprehensive medication review and hazard evaluation ought to be carried out by interdisciplinary team to distinguish the polypharmacy and its unfavorable impacts.[13]

Medication nonadherence may be a major cause of morbidity, particularly in elderly patients. Roughly 10% of hospitalizations may be a result of medicine nonadherence.[14] Our results demonstrated that non adherence to drugs was significantly higher in patients who received ≥5 drugs in group I compared to those who received <5 drugs. In comparison between the polymedicated groups (IB and IIB), non-adherence was significantly higher in IIB group.

Pasina L. et al. [15] reported that low medicine adherence may be a real, complex issue for geriatric patients receiving polypharmacy. They found that the increasing number of drugs endorsed at hospital discharge is related to non-adherence and a high rate of patients did not understand the reason of their medicines. Simplification of drug regimens and decrease of pill burdens as well as way better clarifications of the reason for the medicines ought to be targets for intervention. Delamater [16] reported that among the factors associated with medication adherence, adherence with a simple prescription is higher than that for a more complex prescription.

On the contrary, Grant RW et al. [17] which demonstrated that in their study sample, patients reported very high medicine adherence rates regardless of number of medications endorsed. Among patients on numerous drugs, most patients with suboptimal adherence were perfectly adherent to all but one medication. Unreported side effects and a lack of confidence in immediate or future benefits were significant indicators of suboptimal adherence. Doctors ought to not feel hindered from endorsing multiple agents in arrange to achieve satisfactory control of hyperglycemia, hypertension, and hyperlipidemia.

Moreover, Cárdenas-Valladolid et al [18] study revealed that poor therapeutic adherence in homebound elderly patients receiving polypharmacy may be a serious issue influencing one of each three individuals concerned, and is directly related to caregiver burden, regardless of age, gender, cognitive status or number of drugs administered.

The variation in results were due to problems with tools for the evaluation of adherence as different studies used different tools such as questionnaires, tests, pill count or judgment by research nurse. [18-21] The same variability was in defining polypharmacy, where the researchers used different definitions. [20,22]

Adverse drug reactions happen nearly day by day in health care institutions and can unfavorably influence a patient’s quality of life, often causing significant morbidity and mortality. [23]. Regarding the adverse drug events, our results showed that there was significant difference in the incidence of the following ADEs; arrhythmia, repeated hypoglycemia, orthostatic hypotension, GIT upsets and bleeding tendency between the patients in the two studied groups being higher in the older patients (group II) ($p= 0.007$, 0.012, $p=0.007$, 0.001, 0.008) respectively. Moreover, these ADEs were significantly higher in elderly polymedicated group (IIB) than (IB) group.

These results go hand in hand with the findings of various studies carried out by Rajesh et al. and Pirmohamed et al who reported that the percentage of ADRs found was higher with age and geriatric population. [24,25] Akhideno P et al. [26] showed that the elderly age group, presence of polypharmacy and the presence of multiple comorbidities found to be associated with and predisposed to ADRs in this study. Moreover, Shareef J et al. [27] revealed that the geriatric patients with diabetes had more

associated comorbidities which forces them to get multiple medications leading to more ADRs. In addition, Subeesh VK et al. [28] revealed that the prevalence of polypharmacy is very high among geriatric population in the study site. The study supported the consequences of polypharmacy and was closely related with multiple comorbidity and advanced age.

On the contrary, Min Zhang et al. [29] in their study of variables that anticipate repeat admission for ADRs in geriatric population uncovered that comorbidity, but not advancing age, predicts repeat admission for ADRs.

Khan LM et al. [30] in his retrospective and prospective studies detailed that the highest incidence of ADR (retrospective 15% and prospective 14.5%) was watched in both groups in patients getting more than 10 medications. The frequency of ADR in relation to age in both groups was highest in patients of age >60 years; it was 52.7% in retrospective study and 54.5% in prospective study. The system most commonly included in ADR was gastrointestinal tract 47.4% in retrospective study and 57.6% in prospective study. This studies recognized gastrointestinal system as the foremost habitually affected system by ADRs in both studies.

Conflict of Interest:

We confirm that there are no known conflicts of interest associated with this publication

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