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A NEW TOOL FOR DETECTING ADVERSE EVENTS ASSOCIATED WITH ORAL ANTIDIABETIC AGENTS

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Abstract- In diabetes mellitus, adverse events associated with oral antidiabetics agents may interfere with the patients' health. This paper presents a study to design and validate a questionnaire to identify adverse events associated with oral antidiabetic agents in primary health care units. After design and field testing of the questionnaire, a cross-sectional observational study was conducted by applying the questionnaire through interview to 357 type 2 diabetics in six primary health care units of the central region of Portugal, between January and December 2013. Descriptive and inferential statistics analysis after checking for the normality of the data was performed. Internal consistency was explored using Cronbach's alpha coefficient; the construct validity was assessed through factor analysis after the Kaiser-Meyer-Olkin test (KMO) and Bartlett's test of sphericity. The accepted level of significance was of p <0.05. The questionnaire included 22 adverse events, a KMO value of 0.649, Bartlett test: p <0.000 and Cronbach's alpha= 0.691. Fifty-five percent (55.2%) of diabetics enrolled in the study (mean age of 67.5 ± 9.5 years) were women. The average development time from onset of disease was 9.1 ± 7.2 years. The most widely used oral antidiabetic drugs are biguanides (62.5%) and metformin+vildagliptin (16.8%), as monotherapy and combination therapy, respectively. The most adverse events pointed out by patients were "Arthralgia" (16.8%), "Paresthesia's" (4.5%), "Flatulence" (3.9%) and "Peripheral edema" (2.8%). Testing of the questionnaire revealed good patient's acceptability and comprehensibility, showed acceptable reliability, and that it is easy to apply in primary health care units.

Keywords - Psychometric properties; validity; questionnaire; adverse drugs events.

I. INTRODUCTION

Diabetes mellitus (DM) is a chronic disease with a high prevalence worldwide and truly epidemic proportions. The latest estimates indicate 387 million people living with diabetes, 8.3% of the world population, with an expected increase of 55% by 2035, affecting 592 million people [1]. A large majority, 77% to 80%, live in low- and middle-income countries and are aged between 40-59 years; so, diabetes affects primarily the working population. These key findings are even more alarming when it is estimated that 175 to 179 million people with diabetes are undiagnosed, whilst diabetes being responsible for 5.1 million deaths in 2013 and 4.9 million in 2014. In addition to the loss of human lives, the diabetes expenditure reached on average 11% of overall spending on healthcare [1].

The most common subtype is Type 2 diabetes mellitus (DM2), which affects about 90% of diagnosed individuals [2]. The different therapeutic strategies for DM2 include diet intervention, physical activity and medication, for the control of plasma glucose levels (HbA1c $\leq$ 6.5%) [3, 4, 5].

Currently, drug therapy with oral antidiabetic agents (OAs), is capable of inducing normoglycemia levels able to decrease the risk of complications associated with this disease [6]. However, it is also known that the various existing oral antidiabetic agents may trigger a large number of adverse events, either alone or in combination [7].

Some of these tolerability and safety issues related to the OAs are reported by patients and can influence negatively satisfaction from treatment, glycemic control, or the therapeutic adherence and maintenance [8].

The most common adverse reactions are gastrointestinal, such as diarrhea, flatulence, abdominal pain, dyspepsia, gastritis, bloating, weight gain and hypoglycemic episodes. Less common are headaches, cough, and flu and back pain [9, 10].

Despite the awareness about adverse reactions and tolerability issues associated with OAs, its prevalence and impact on the daily lives of patients is not known. These adverse reactions are reported at the level of clinical trials, which often do not reflect the use of medicines in the real world [11].

In spite of the limitations, studies in a real context can generate valuable clinical information in terms of effectiveness and safety profile of OAs to complement clinical trials [12].

In this perspective, patients play an important role monitoring adverse events resulting from the use of OAs, as has been widely recognized by health systems [13]. This information can enable the adoption of measures that promote adherence and maintenance of the therapeutics and improve the quality of life of patients with DM2.

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The aim of this study is to design and validate a questionnaire suitable for administration in primary health care, capable of identifying adverse events associated with the use of OAs, perceived and self-reported by the patients.

II. MATERIAL AND METHODS

Study Design

The study has been carried out in two phases: phase 1 consisted of the design (content and structure) of the questionnaire for assessment of adverse events associated with OAs and the second phase included the evaluation of its psychometric properties.

Phase 1: Questionnaire design

During the initiation of Phase 1 a review of the scientific literature was conducted on adverse events associated with OAs approved and marketed in Portugal. The data obtained enabled us to list all adverse events reported for each drug, which resulted in a collection of about 30 different adverse events. For the purposes of this study, we added to this list of 30 adverse events, a Likert scale with four levels to assess the frequency and intensity of adverse events self-perceived by patients, namely: 1-Never/None; 2-Rarely/Low intensity; 3-Often/Strong intensity; 4-Always/Severe [14].

The draft version of the questionnaire was evaluated for content validity, following on the recommendations of Bryman & Cramer (2004) [15]; thus, the questionnaire was analyzed by a panel of experts for a critical appraisal in terms of terminology and degree of adequacy to the theoretical construct to be measured. A final version of the questionnaire containing 26 items of adverse events was obtained, after having taken in consideration the suggestions proposed by the panel of experts and conducting a field testing (pre-test) to evaluate the acceptability and comprehensibility of the questionnaire.

Phase 2: Evaluation of the psychometric properties of the questionnaire

Following on the design of the questionnaire, the authors proceeded with exploratory factor analysis to determine the psychometric properties of the instrument. Given the number of items for the measured variable and to ensure the reliability of the factor analysis, the sample size simultaneously met the criteria of having at least five subjects assessed per item and not less than 100 individuals [16].

In terms of the psychometric properties, the acceptability and sample distribution were explored on the basis of the frequency distribution. Reliability, as the degree of internal consistency, was measured using the Cronbach alpha coefficient, which is considered acceptable between 0.70 and 0.95 [17].

The adequacy of the sample was assessed using the Kaiser-Meyer-Olkin test (KMO) and the Bartlett's test of sphericity. As KMO should vary from 0 to 1, different authors advice an average value of 0.50 for further statistical analysis [18, 19]. Regarding the pattern of correlation between variables, the factor loadings should show most of the coefficients' values above 0.30 [19].

The anti-image correlation matrix was also analyzed, which is another measure of sampling adequacy for each variable: low values (<0.5) of the main diagonal indicate that the elimination of the variable should be considered [19].

The accepted level of significance was $p < 0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 22.0 for Windows.

Subjects

A total of 357 DM2 patients were enrolled in the study (an observational and cross-sectional study) (95% confidence interval for a 0.05 margin of error) and were recruited from the Diabetes medical appointments in primary health care of Coimbra, Portugal (January-December 2013). The inclusion criteria to participate in the study consisted of clinical diagnosis of DM2 for at least one year; exclusive oral antidiabetic agents; over 18 years of age, and cognitive ability to answer the survey questions. Information was gathered from all patients by individual interview using the questionnaire for assessment of adverse events associated with (daily) oral antidiabetic agents. Sociodemographic (gender, age, educational level, employment status, family status, household and socioeconomic status) and clinical data (onset of diabetes, body mass index (BMI), glycated hemoglobin (HbA1c)) were also collected.

An explanation of the study was given to the patients, and all were asked to sign a consent form before answering the questionnaire.

III. RESULTS

The study was conducted after the approval of the Regional Health Administration Center, IP and the Ethics Committee of the Medical School of the University of Coimbra. Of the 357 (non-insulin dependent) diabetic patients who participated in the study, 55.2% are women, the mean age of the population studied is 67.5 ± 9.5 years and a total of 55.7% can only read or write. Most are retired (78.2%), married (72.0%) and living together (85.4%), on the basis of a low (48.5%) and median (51.5%) socioeconomic status.

The average development time from onset of disease was 9.10 ± 7.2 years, ranging from 1 to 42 years of diagnosis. Only 11.8% of the subjects had a normal BMI value (mean BMI of 30.57 ± 4.85 kg/m^2). The mean HbA1c level was equal to 6.65 ± 0.88%, a value within the normal range [20].

The most widely used oral antidiabetic agents in monotherapy belong to the class of Biguanides (Metformin 62.5%) and sulfonylureas (gliclazide, glimepiride and glibenclamide 31.1%). In dual combination therapy, the options fall into the pool metformin + vildagliptin (16.8%) and metformin + sitagliptin (12%).

Acceptability and Distribution

The instrument was well accepted by patients who found it comprehensible and easy to use, taking 10 minutes in average to complete it. Also, there were no missing data, demonstrating the adaptation of the instrument to the level of knowledge of patients.

The percentage of individuals scoring near the lower limit of responses (1-Never/None; 2-Rarely/Low intensity) was much higher than those falling at the opposite limit (3-Often/Strong intensity; 4-Always/Severe). This distribution of adverse events clearly expresses a floor effect, which was more evident in adverse events such as "anaemia", "diarrhoea", "epigastric pain", "alterations in the liver", and "respiratory infections". Patients reported more frequently adverse events (level 3 and level 4) such as "joint pain" (16.8%), "paraesthesia" (4.5%), "flatulence" (3.9%), "oedema

peripheral" (2.8%), "changes in vision" (2.5%), "weight gain" (2%) and "headache" (1.7%) (Table 1).

TABLE 1: Distribution of adverse events.

Adverse Events	Never	Rarely	Often	Always
	None (1)	Low intensity (2)	Strong intensity (3)	Severe (4)
1. Weight gain	255 (71.4%)	95 (26.6%)	7 (2.0%)	
2. Anaemia	330 (92.4%)	27 (7.6%)		
3. Bruising (Amendment coagulation)	307 (86.0%)	48 (13.4%)	2 (0.6%)	
4. Hair loss (alopecia)	312 (87.4%)	43 (12%)	2 (0.6%)	
5. Skin blemishes, without allergies (Skin Reactions)	333 (93.3%)	23 (6.4%)	1 (0.3%)	
6. Allergic reactions (itchy skin, nose or eyes, itching, hives, skin rash)	235 (65.8%)	117 (32.8%)	5 (1.4%)	
7. Belching much (aerophagia)	274 (76.8%)	79 (22.1%)	4 (1.1%)	
8. Diarrhoea	311 (87.1%)	46 (12.9%)		
9. Swollen belly (abdominal distension)	263 (73.7%)	91 (25.5%)	2 (0.6%)	1 (0.3%)
10. Stomach pain (Pain Epigastric)	317 (88.8%)	40 (11.2%)		
11. Gases (Flatulence)	184 (51.5%)	159 (44.5%)	14 (3.9%)	
12. Feeling sick (nausea)	328 (919%)	27 (7.6%)	2 (0.6%)	
13. Vomiting	329 (92.2%)	25 (7%)	3 (0.8%)	
14. Changes in the liver (Increase of transaminases)	328 (91.9%)	29 (8.1)		
15. Joint pain (Arthralgia)	119 (33.3%)	178 (49.9%)	59 (16.5)	1 (0.3%)
16. Lack of strength	256 (71.7%)	96 (26.9%)	5 (1.4%)	
17. Loss of appetite (anorexia)	314 (88%)	41 (11.5%)	2 (0.6%)	
18. Headache	257 (72%)	94 (26.3%)	6 (1.7%)	
19. Tingling (paraesthesia)	180 (50.4%)	161 (45.1%)	16 (4.5%)	
20. Somnolence	307 (86%)	49 (13.7%)	1 (0.3%)	
21. Dizziness	271 (75.9%)	83 (23.2%)	3 (0.8%)	
22. Changes in vision	189 (52.9%)	159 (44.5%)	9 (2.5%)	
23. Shortness of breath (dyspnoea)	328 (91.9%)	27 (7.6%)	2 (0.6%)	
24. Respiratory Infections	347 (97.2%)	10 (2.8%)		
25. Cold (nasopharyngitis)	294 (82.4%)	60 (16.8%)	3 (0.8%)	
26. Swelling of legs (Peripheral Oedema)	256 (71.7%)	91 (25.5%)	9 (2.5%)	1 (0.3%)
Total	**357 (100%)**			

Reliability

Cronbach's alpha coefficient for the total 26 items (adverse events) was 0.691 and all items considered individually showed satisfactory internal consistency, ranging from 0.666 to 0.694. The intra-class coefficient of correlation (ICC) obtained varied between 0.643 and 0.735, which indicates an acceptable internal consistency of the questionnaire [17].

Exploratory factor analysis

Construct validity was assessed according to the exploratory factor analysis protocol [21] for the 26 items of adverse events. Support for the validity of factor analysis was demonstrated by the existence of correlations between variables, confirmed by a value of KMO equal to 0.649 and the Bartlett test ($\chi 2$ = 1039.079; df = 325, p <0.001). Both measures indicate that it is appropriate to proceed with the factor analysis [18]. We use factor analysis with orthogonal varimax rotation and free factor extraction to all responses of the 26 items of the questionnaire.

The results showed the existence of 10 eigenvalues greater than 1, thus, 10 factors were retained explaining 56.84% of the total variance. All items had a factor loading above 0.3 in at least one factor with the exception of item "Tingling" that saturates in factor 1 and 9, and item "Alterations in the liver" which had a factor loading of 0.214 (<0.3). The anti-image matrix showed values on the main diagonal ranging between 0.396 and 0.848 and all values outside this diagonal were small (absolute maximum value of 0.155). The items "Changes in vision", "Respiratory infections", "Alterations in the liver" and "Skin blemishes without allergies" scored below 0.5 on the main diagonal.

In terms of discriminant validity, significant associations were found between the different adverse events and the sociodemographic (gender and age) and clinical variables (DM2 duration, BMI and HbA1c). Women reported a higher number of adverse events than men and this difference is statistically significant (p <0.05) in 12 of the 26 adverse events.

In terms of age, individuals between 65 and 74 years old, are those who identified more adverse events, although this difference is not significant in comparison to the other age groups (p> 0.05).

For the clinical variables, we found that patients with the lowest duration of disease (≤10 years) had more adverse events than others. This seems to indicate that those individuals having DM2 for a longer period of time show less discomfort and are more used to its clinical manifestations.

In relation to BMI, a positive significant association (p <0.05) was found between obesity and the adverse events "Weight gain" and "Lack of strength".

Furthermore, individuals with HbA1c values above the reference values, showed more adverse events than individuals with normal values, although not statistically significant (p> 0.05).

IV. DISCUSSION

In this study we found that diabetic patients identify with relative ease the various adverse events associated with oral antidiabetic agents. The acceptability and comprehensibility of the questionnaire was evident, however, the distribution of

adverse events was uneven, since the respondents showed a tendency to concentrate answers on Level 1 and Level 2. Given that the mean age of this population of study is 67.48 years, with a development time from disease diagnosis of 9.10 years on average, it seems that there is an adaptation to the drug and its effects.

According to the international medical terminology MedDRA [22], the most reported adverse events belong to gastrointestinal disorders (flatulence, aerophagia and abdominal distension), nervous system disorders (paresthesia and headache), general disorders and administration site conditions (peripheral edema and lack of strength), musculoskeletal and connective tissue disorders (joint pain), immune system diseases (allergic reactions) and diseases of metabolism and nutrition disorders (weight gain). Our results are in accordance with other authors on the various adverse events perceived by patients with type 2 diabetes, either in oral antidiabetic agents in monotherapy or in combination [23-27].

The analysis of reliability of the initial version of the questionnaire with 26 items of adverse events resulted in a Cronbach's alpha of 0.691, showing a reasonable internal consistency of the questionnaire [17]. However, the exploratory factor analysis (KMO = 0.649 and $p < 0.001$) led to the reduction of the questionnaire to 22 items, with the exclusion of items such as "Changes in vision", "Respiratory infections", "Alterations in the liver" and "Skin blemishes without allergies". The values of these variables in the exploratory factor analysis do not fit the structure defined by other variables. The final version of the questionnaire was completed with 22 items of adverse events with values and acceptable quality [16-19].

The evaluation of the discriminant capacity of the questionnaire resulted in an evident difference between men and women. Overall, women seem to be more susceptible to adverse events and also show a higher perception of adverse events. Our study shows that there seems to be a difference in gender in terms of health behavior, which is also confirmed by other studies [28-30].

Obese subjects and those with normal BMI show a different perception of adverse events, as well as individuals with a normal or high level of HbA1c.

V. CONCLUSIONS

The questionnaire for assessment of adverse events associated with oral antidiabetic agents seems appropriate and easy to apply in the context of primary health care. Due to the lack of detailed information on the daily/chronic use of this large group of medications, the authors suggest the use of this instrument in future research to strengthen the validation process and also to improve the evaluation of effectiveness of oral diabetes therapy.

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