

Article

Prevalence of Adverse Drug Events in Severely Obese Adults and Associated Factors: Clinical Trial Baseline Results

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Abstract: Drugs are the most widely used therapeutic tool for treatment of diseases. However, misuse can lead to an adverse drug event (ADE) in susceptible individuals such as those that are severely obese. This study aimed to describe the frequency of ADEs, the associations of ADEs with anatomical therapeutic chemical classes and their respective frequency, estimate the prevalence of ADEs, and analyse factors associated with ADE in adults with severe obesity. Cross-sectional analysis of baseline data from a randomized clinical trial in the central-western region of Brazil. A total of 150 individuals aged 18–65 years with a Body Mass Index of 35 kg/m² were included. The outcome variable was the presence of ADE and the explanatory variables were socio-demographic factors, lifestyle, health, and medication use. ADEs were associated with use of drugs for the digestive tract and metabolism ($p < 0.001$) and the cardiovascular system ($p < 0.001$). The prevalence of ADEs was 32.67% ($n = 49$) and associated with the age range 40 to 49 years ($p = 0.033$), diabetes ($p = 0.004$), multimorbidities ≥ 4 ($p = 0.009$), self-medication (0.031), and presence of potential drug interactions (0.017). The prevalence of ADEs was high and was associated with drugs commonly used in treatment of obesity-related morbidities and self-medication. The introduction of a pharmacist to multi-professional teams can improve medication safety for severely obese patients.

Keywords: severe obesity; adverse drug events; drug utilization reviews; randomized controlled trial; pharmacoepidemiology; diabetes mellitus; multimorbidities; self-medication

1. Introduction

The drug is the most widely used therapeutic tool for the diagnosis, prophylaxis, and treatment of diseases [1]. Undeniably, drug therapy has evolved through history and has improved people's quality of life [2]. However, misuse of medications can lead to adverse drug events (ADE) [3], which are defined as instances of harm to the patient that result from the use of drugs in doses commonly used for the prophylaxis and treatment of disease as well as from errors in their use [3].

Some risk factors of ADEs are known, such as age, multimorbidities, and polypharmacy [1]. Polypharmacy [4] is a major challenge faced by health professionals who care for patients with chronic diseases [5]. The presence of multimorbidities is associated with increased medication use, and

individuals with multimorbidities are almost 15 times more likely to develop an ADE compared with healthy individuals [6].

Another potential risk factor for ADEs is obesity, a condition of abnormal or excessive fat accumulation in adipose tissue [7] that can lead to the development of multimorbidities that require the chronic use of drugs, such as diabetes, hypertension, cardiovascular disease, dyslipidaemia, osteoarticular problems, and a number of cancers [8,9]. Moreover, obesity can also reduce the drug efficacy [10], which may lead to potential drug-related problems. Severe obesity, characterised by a body mass index (BMI) ≥ 35 kg/m², is the fastest growing BMI category in the world and is associated with increased morbidity and mortality rates [9].

Studies on drug use in obese individuals are scarce, and existing studies focus on potential therapeutic targets of treatment [11–13]. Regarding the safety of medication use in obese people, the available literature is limited to describing adverse events associated with obesity treatment [14] without considering the use of concomitant therapy. Studies on ADEs in obese individuals, and in particular, severely obese individuals, are rare. Research on the use of medicines is particularly important to fill the gap regarding medication safety in real life contexts [15].

Given that 35% of the US population is obese, it can be extrapolated that, of the 16,651 drug-related deaths that occur annually in the US, approximately 5800 obese individuals die from ADEs every year [16]. Although similar data have not been found in other countries, the alarming global rate of growth of severe obesity in recent years [9] and the risk of ADEs for obese individuals make the development of research on this subject vital. Here, we hypothesize that severely obese individuals are more susceptible to experiment an ADE because they have multimorbidities and use many drugs. Considering the gap observed in the literature, the objectives of this study were (a) to describe the frequency of ADEs by organs and systems; (b) to describe the associations with ADEs of Anatomical Therapeutic Chemical (ATC) classes and their respective frequency; (c) estimate the prevalence of ADEs; and (d) analyse the possible factors associated with an ADE in adults with severe obesity.

2. Materials and Methods

2.1. Setting and Study Design

This study was a cross-sectional analysis of baseline data from the DieTBra Trial (Effect of Nutritional Intervention and Olive Oil in Severe Obesity: Randomised Controlled Trial), which aimed to evaluate the effects of nutritional treatment on inflammation, weight loss, and biochemical markers in severely obese individuals with records in [ClinicalTrials.gov](https://clinicaltrials.gov) study NCT02463435. Patients were referred from the Brazilian Unified Health System (UHS) of primary healthcare to the Nutrition and Severe Obesity Outpatient Clinic in a large university hospital in the Central-West Region of Brazil. We excluded from the study individuals that had already undergone bariatric surgery; were under actual nutritional treatment for weight loss or had been in the previous 2 years; were using antiobesity drugs; had HIV/AIDS, heart/kidney/hepatic insufficiency, chronic obstructive pulmonary disease, or cancer; and pregnant women. Further methodological details can be found in DieTBra Trial articles with baseline data published elsewhere [17,18].

In the trial protocol, all drug use variables and analyses were pre-specified in baseline data and approved by the Ethical Committee. Data regarding drug use were collected by a trained pharmacist according to a standard operational procedure from June 2015 to February 2016. All the participants gave their written consent to participate in this study, conforming to the Helsinki declaration. This study was approved by the Local Research Ethics Committee with registration number 1.545.504.

2.2. Subjects

The subjects in the study included individuals aged 18 to 65 years with BMI ≥ 35 kg/m² [7], who were referred from primary care to an outpatient clinic specialising in the care of severely obese patients. Individuals residing outside the metropolitan area who had already undergone bariatric surgery that

reduced more than 8% of their weight in the last three months, who had received treatment, or who were currently being treated for obesity at the same outpatient clinic as well as pregnant women, infants, and those with special needs were excluded. During the follow-up, we had two withdrawals: one patient was hospitalized due to pneumonia and another claimed lack of time to attend the clinic visits.

2.3. Variables

The outcome variable was the presence of ADEs [3], as assessed by the question: “Do you notice any different symptoms with the use of this medication?” This question was asked for each medication used by the patient and categorised as “yes” when the patient had at least one symptom suggestive of ADEs and “no” when there was no symptom. Symptoms were then categorised according to the classification of organs and systems and the Medical Dictionary for Regulatory Activities [19].

The analytical variables were divided into four categories: sociodemographic, lifestyle, health condition, and drug use.

2.3.1. Sociodemographic

Sociodemographic factors included sex, age, years of study, skin colour, relationship status, and economic class determined by Brazil’s standard economic classification criteria [20].

2.3.2. Lifestyle

The consumption of alcoholic beverages was estimated by asking patients about the amount of alcohol they had consumed the previous week [21]. Smoking responses were categorised as “non-smoker”, “ex-smoker”, or “smoker” [22].

2.3.3. Health

BMI was calculated by dividing body weight in kilograms by the square of height in meters. Patients with BMI ≥ 35 kg/m² and ≥ 40 kg/m² were classified as having grade II and grade III obesity, respectively [7]. Arterial hypertension was classified by blood pressure levels of $\geq 140/90$ mm/Hg [23] and/or the use of antihypertensive drugs. Diabetes mellitus (DM) was classified by fasting plasma glucose values ≥ 126 mg/dL [24] and/or use of antidiabetic drugs. Hypercholesterolemia was classified by the presence of one or more of the following conditions: isolated hypercholesterolemia, isolated hypertriglyceridemia, mixed hyperlipidaemia or low-density lipoprotein [25], or use of anti-lipemic drugs. Multimorbidities [7] consisted of the number of diseases reported by the patient in the interview.

2.3.4. Drug Use

The use of drugs that cause weight gain [8,10,26,27] and polypharmacy, which is the practice of using five or more drugs [28], were categorised as “yes” or “no”. Self-medication [29] was assessed by asking, “Do you have a prescription?” for each drug used by the patient, and answers were classified as “yes” or “no” according to the patient’s habitual use of non-prescription drugs. The drugs used by the patient were classified according to the ATC classification system [30]. Non-ATC and phytotherapeutic drugs were categorised as non-classifiable, as they are not included in the ATC classification. Potential drug interactions (PDI) were estimated by searching the Micromedex® [31] database for all drugs used by the patient. Subsequently, the PDI was reclassified when at least one PDI was identified and considered absent when no PDI was identified.

2.4. Data Collection

All data collection was performed by a trained multiprofessional team according to the standard operating procedures of the clinical trial. Sociodemographic, drug therapy, and anthropometric data were collected by a psychologist and a physiotherapist, a pharmacist, and a nutritionist, respectively.

2.5. Statistical Analyses

The association of variables was tested by Pearson’s chi-square test, Fischer’s exact test, or linear trend chi-square test. Multiple Poisson regression was performed by hierarchical model, and variables with p -value < 0.20 in the bivariate analysis were included in the multiple model. The first level included sociodemographic and lifestyle variables, the second level included health, and the third level included the use of medication. Variables that did not retain an association were removed from the final model. The measure of effect was presented as the prevalence ratio, with a 95% confidence interval (CI). All analyses were performed using Stata software, version 14, with a significance level of 5%.

3. Results

Among the 150 subjects included in the study, the prevalence of ADEs was 32.67% ($n = 49$) (95% CI 41–58). As shown in Table 1, the symptoms most commonly reported as ADEs were related to gastrointestinal tract disorders, one-third of which were stomach aches ($n = 10$, 33.33%), followed by nausea and vomiting ($n = 9$, 30.00%). Central nervous system-related adverse effects ranked second, the most frequent being drowsiness ($n = 15$, 75.00%) and headaches ($n = 2$, 10.00%).

Table 1. Frequency of adverse drug events in severely obese adults, by organ and system classification.

Adverse Drug Events	<i>n</i> (%)
Gastrointestinal disorders	30 (61.22)
Nervous system disorders	20 (40.82)
Skin and subcutaneous tissue disorders	3 (6.12)
Cardiac disorders	2 (4.08)
General disorders and administration site conditions	2 (4.08)
Renal and urinary disorders	2 (4.08)
Respiratory, thoracic, and mediastinal disorders	2 (4.08)
Blood and lymphatic system disorders	1 (2.04)
Metabolism and nutrition disorders	1 (2.04)
Musculoskeletal, connective tissue, and bone disorders	1 (2.04)
Reproductive system and breast disorders	1 (2.04)

The therapeutic classes that were associated with ADEs were the alimentary tract and metabolism ($p < 0.001$) and the cardiovascular system ($p < 0.001$) (Table 2).

Table 2. Frequency and association of drug groups by ATC classification involved in adverse drug events in adults with severe obesity.

ATC Classification	Total <i>n</i> (%)	ADE Presence	<i>p</i> Value
A Alimentary Tract and metabolism	57 (38.00%)	30 (52.63%)	0.000 *
B Blood and forming blood organs	11 (7.33%)	6 (54.55%)	0.108 *
C Cardiovascular system	65 (43.33%)	32 (49.23%)	0.000 *
D Dermatological	0	0	0
G Genito urinary system and sex hormones	12 (8.00%)	3 (25.00%)	0.406 **
H Systemic hormonal preparations, excluding sex hormones and insulins	10 (6.67%)	5 (50.00%)	0.226 *
J Antiinfectives for systemic use	6 (4.00%)	2 (33.33%)	0.640 **
L Antineoplastic and immunomodulating agents	0	0	0
M Musculo-skeletal system	97 (64.67%)	37 (38.14%)	0.053 *
N Nervous system	86 (57.33%)	29 (33.72%)	0.750 *
P Antiparasitic products, insecticides and repellents	1 (0.67%)	0 (0%)	-
R Respiratory system	17 (11.33%)	5 (29.41%)	0.761 *
S Sensory organs	1 (0.67%)	0 (0%)	-
V Various	0	0	0
NC Non-Classifiable	16 (10.67%)	8 (50.00%)	0.118 *

* Chi-squared; ** Fischer; ATC: Anatomical Therapeutic Chemical Classification.

The variables associated with ADE in the bivariate analysis were age group of 40 to 49 years ($p = 0.030$), arterial hypertension ($p = 0.001$), diabetes mellitus ($p = 0.001$), number of multimorbidities

($p = 0.001$), use of drugs that cause weight gain ($p = 0.011$), polypharmacy ($p < 0.001$), and potential drug interactions ($p < 0.001$) (Table 3).

Table 3. Frequency of adverse drug events and their association with sociodemographic variables, lifestyle, health profile, and drug use in severely obese adults ($n = 150$).

Variables	Total n (%)	Presence of ADE	PR (CI 95%)	p-Value
Sex				
Male	22 (14.67)	6 (27.27)	1.00	0.559 *
Female	128 (85.33)	43 (33.59)	1.23 (0.59–2.54)	
Age				
18–39	76 (50.67)	18 (23.68)	1.00	0.030 **
40–49	53 (35.33)	22 (41.51)	1.75 (1.04–2.93)	
≥50	21 (14.00)	9 (42.86)	1.80 (0.95–3.43)	
Skin Color				
White	46 (30.67)	16 (34.78)	1.15 (0.68–1.93)	0.734 *
Brown	83 (55.33)	25 (30.12)	1.00	
Black	21 (14.00)	8 (38.10)	1.26 (0.66–2.39)	
Economic Class				
Class A/B	34 (22.67)	12 (35.29)	1.20 (0.68–2.09)	0.484 *
Class C	92 (61.33)	27 (29.35)	1.00	
Class D/E	24 (16.00)	10 (41.67)	1.41 (0.80–2.51)	
Lives with Partner				
No	55 (36.67)	19 (34.55)	1.09 (0.68–1.75)	0.709 *
Yes	95 (63.33)	30 (31.58)	1.00	
Smoking				
No	101 (67.33)	32 (31.68)	1.00	0.712 *
Yes	49 (32.67)	17 (34.69)	1.09 (0.67–1.77)	
Alcohol Intake (n = 84)				
No	13 (15.48)	3 (23.08)	1.00	0.301 ***
Yes	71 (84.52)	27 (38.03)	1.64 (0.58–4.67)	
Body Mass Index				
35–39	27 (18.00)	11 (40.74)	1.31 (0.77–2.23)	0.323 *
≥40	123 (82.00)	38 (30.89)	1.00	
Arterial Hypertension				
No	65 (43.33)	12 (18.46)	1.00	0.001 *
Yes	85 (56.67)	37 (43.53%)	2.35 (1.33–4.15)	
Diabetes				
No	90 (60.00)	20 (22.22)	1.00	0.001 *
Yes	60 (40.00)	29 (48.33)	2.17 (1.36–3.47)	
Hypercholesterolemia				
No	94 (62.67)	29 (30.85%)	1.00	0.539 *
Yes	56 (37.33)	20 (35.71%)	1.15 (0.72–1.84)	
Comorbidities				
≤3	89 (59.33)	20 (22.47)	1.00	0.001 *
≥4	61 (40.67)	29 (47.54)	2.11 (1.32–3.38)	
Drugs that Cause Weight Gain				
No	106 (70.67%)	28 (26.42%)	1.00	0.011 *
Yes	44 (29.33%)	21 (47.73%)	1.80 (1.15–2.81)	
Self-Medication				
0	23 (15.33%)	6 (26.09%)	1.00	0.178 *
1–2	89 (59.33%)	26 (29.21%)	1.11 (0.52–2.40)	
≥3	38 (25.33%)	17 (44.74%)	1.71 (0.78–3.72)	
Polypharmacy				
No	101 (67.33%)	19 (18.81%)	1.00	<0.001 *
Yes	49 (32.67%)	30 (61.22%)	3.25 (2.04–5.17)	
Potential Drug Interactions				
No	75 (50.00)	12 (16.00)	1.00	<0.001 *
Yes	75 (50.00)	37 (49.33)	3.08 (1.60–5.91)	

* Pearson’s Chi-square; ** Linear trend Chi-square; *** Fischer Exact Test.

The variables that remained associated with ADE after multiple analysis were: age group 40 to 49 years ($p = 0.033$), diabetes mellitus ($p = 0.004$), number of multimorbidities ≥ 4 ($p = 0.009$), self-medication with three or more drugs ($p = 0.031$), and potential drug interactions ($p = 0.017$) (Table 4).

Table 4. Multiple regression of possible factors associated with adverse drug events in severely obese adults ($n = 150$).

Variables	Adjusted Prevalence Ratio	CI 95% Adjusted	p Value *
Age			
18–39	1.00		
40–49	1.75	1.04–2.93	0.033
≥ 50	1.81	0.95–3.43	0.069
Diabetes			
No	1.00		
Yes	2.03	1.26–3.29	0.004
Comorbidities			
≤ 3	1.00		
≥ 4	1.91	1.17–3.11	0.009
Self-medication			
0	1.00		
1–2	1.45	0.72–2.89	0.290
≥ 3	2.15	1.07–4.35	0.031
Potential drug interactions			
No	1.00		
Yes	2.21	1.15–4.26	0.017

* Poisson Regression.

4. Discussion

Judging by the literature review, this study pioneers a risk factor analysis of ADEs in severely obese individuals. The high prevalence of ADEs in these individuals was associated with age, diabetes mellitus, number of multimorbidities, self-medication, and potential drug interactions. These findings are relevant to the clinical area of obesity treatment and to multi-professional teams motivated to avoid occurrences of ADEs. Especially considering that the prevalence of severe obesity has significantly increased in the world population, accompanied by rising health care costs, worsening quality of life for individuals, and increased mortality [9,32], these results highlight the importance of investigating patterns of drug use and of ADEs in severely obese patients.

This study found a high prevalence of ADE, but no studies were found that evaluate this outcome in individuals with BMI ≥ 35 kg/m² or in obese people in general. A similarly high prevalence of ADEs also exists among people with chronic diseases such as HIV (52.7%) [33] and among the elderly in the United States (42.9%) [34].

Regarding ADEs classified by organs and systems, results from our study were similar to those found in other studies. About one-third reported gastrointestinal tract (GIT) symptoms, and 10% reported central nervous system (CNS)-related symptoms [33,35]. The high prevalence of GIT symptoms can be explained by obesity itself, which is a risk factor for hepatic steatosis [36,37], abdominal pain, nausea, vomiting, and diarrhoea [37]. In addition, hepatic steatosis may be associated with changes in drug metabolism, which contribute to the manifestation of GIT-related symptoms [38]. Although CNS-related symptoms have not yet been physiologically elucidated, obesity has been associated with sleep disorders [39], which could explain the sleepiness presented by the patients in our study.

Regarding ATC classes and their association with ADEs, the results of our study are in line with others on adults with chronic diseases, showing a higher prevalence of ADE among those who

use drugs for the digestive tract and metabolism and for the cardiovascular system [35,40]. These associations can be interpreted two ways. In the treatment of diabetes, oral antidiabetics and insulin are not only common but also high-alert medications precisely because they present a risk of harm to the patient, such as hypoglycaemia [41]. The association between ADEs and this class of drugs in several groups of individuals is well described in the literature [42,43]. Additionally, metformin use in severely obese patients increases the chance of developing hepatic steatosis by almost one-and-a-half times [36], which may partly explain the GIT-related symptoms in our study. Although considered safe, metformin use, especially in obese individuals, should be monitored. Liver function tests and imaging tests should be ordered at the beginning of treatment to assess progression of liver injury.

An age-adjusted analysis showed increased ADE among 40- to 49-year-olds compared with 18- to 39-year-olds. This association, however, did not occur among individuals older than 50, remaining within the limit of significance. As there are no previous studies with which to compare our results, we drew a parallel to studies on the elderly with chronic diseases, a systematic review of which showed a higher prevalence of ADEs in these individuals [44].

The association of ADEs with DM in our study has also been observed in India [45]. This association can be explained by two distinct mechanisms. DM is a condition that can affect the pharmacokinetics and pharmacodynamics [46] of medications and contribute to the occurrence of ADEs. DM treatment is also a risk factor for ADE, as antidiabetic drug use is the third leading cause of hospitalization in the United States [47]. One ADE in diabetes patients is hypoglycaemia, which can lead to severe neurological damage and hospitalization [48]. It is noteworthy that DM is prevalent in severely obese individuals [48], and MI for these patients can be even more severe than for non-obese people if they are not effectively monitored by a multi-professional team. Monitoring these patients may minimise the occurrence of severe ADEs and provide much safer therapy [47]. The adoption of a validated tool to evaluate patients at risk for the development of severe hypoglycaemia is suggested [4].

We observed a significant association of ADEs with multimorbidities and PDI in severely obese individuals, clinical variables that are interconnected. Although no previous studies about ADEs among the obese or severely obese have been identified, a systematic review has shown that individuals with multimorbidities are twice as likely to experience an ADE [49]. These findings may be explained by the fact that these patients require complex health care and therapeutic regimens with many medications, making them more susceptible to ADEs [50]. Likewise, no studies evaluating PDI that resulted in ADEs in severely obese patients were found. Considering the predictability of some PDI [51], greater attention is needed from health professionals in the management of individuals at risk of ADEs due to PDI. The same attention is needed for those with multimorbidities.

The association between ADEs and self-medication in severely obese patients is consistent with a systematic review of the elderly, among whom an increased risk of ADEs in those who self-medicate was observed [52]. In Germany, it was reported that 4% of hospitalizations of the elderly were associated with ADEs caused by self-medication [53]. In both studies, most patients complained of GIT-related symptoms [52,53], similar to the results of our study. These results may be partially attributable to the fact that self-medication is a common behaviour in patients with multimorbidities [52].

Socio-demographic variables were not associated with ADEs in obese patients; therefore, the results of our study are in line with those of other studies conducted in Brazil [35,54]. No other studies were found that analysed the impact of BMI as a risk factor for ADEs in both obese and chronically ill patients. Clinical variables are more associated with ADEs compared with sociodemographic variables [35].

The strength of our study is that it is a baseline analysis of a randomised clinical trial that followed rigorous methodological criteria and met all the precepts of good clinical research practice. The number of severely obese individuals is relevant, considering the prevalence of this class of obesity reaching 0.64% in men and 1.6% in the world [32], with the highest health risks in this group.

A possible limitation of this research is recall bias because of a reliance on the patient as a source of information about ADEs. However, other studies have already highlighted the value of patients

self-reporting medication use, as their reports provide important details regarding ADEs, such as the circumstances of their drug use [55].

As obesity is a risk factor for the development of other chronic diseases, more studies assessing the causality of ADEs are needed to elucidate important aspects that differentiate a new symptom from a new ADE. Drug use in individuals with severe obesity should be carefully analysed, since it is a population with multimorbidities, usually cared for by a team of health professionals. This fact may contribute to the chronic use of multiple medications, which in turn may contribute to the manifestation of ADEs. Pharmacoepidemiological studies involving the pharmacotherapy of other morbidities in obese patients are scarce in the literature, so the results of our study may help in the management of drug use safety in severely obese individuals.

5. Conclusions

The prevalence of ADEs was high, affecting more than one-third of patients and was associated with drugs commonly used in treatment of obesity related morbidities and self-medication. Considering the relevance of medication safety to the world health agenda [1], the introduction of a pharmacist to the multi-professional teams leading structured medication reviews can improve medication safety for severely obese patients.

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