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PREVALENCE OF HYPOGLYCEMIA, TREATMENT SATISFACTION, ADHERENCE AND THEIR ASSOCIATIONS WITH GLYCEMIC GOALS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS TREATED WITH SULFONYLUREAS: FINDINGS FROM THE REAL-LIFE EFFECTIVENESS AND CARE PATTERNS OF DIABETES MANAGEMENT (RECAP-DM) IN ROMANIA

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Abstract

Background and aims: *The aim of this study was to assess the prevalence and evaluate the impact on several treatment and quality of life parameters of hypoglycemia in type 2 diabetes mellitus patients treated with sulfonylureas (SU) in Romania. Secondary objective was to determine the proportion of patients attaining haemoglobin A1c (HbA1c) target of <7%.* ***Material and method:*** *This was a multi-center, observational study using retrospective clinical chart and laboratory parameters review, and a cross-sectional survey in Romania. The sample in this study consisted of 385 patients. Socio-demographic and clinical variables were compared between patients with inadequate and adequate control.* ***Results:*** *The mean age of all enrolled subjects was 65.37 (33-87) years. The average BMI was 30.44 kg/m2. Mean diabetes duration was 7.76 (6 months -32) years with the mean age of diabetes at diagnosis of 57.75 (31-85) years. HbA1c was recorded for 238 subjects with mean value of 7.12 (4.8-10.97) %.* ***Conclusions:*** *The prevalence of hypoglycaemia in SU treated patients was 42.2%. Highest prevalence was in the 50-60 age category, at 49.2% and lowest among the eldest subjects (>70 years), at 38.6%. Prevalence of patients at the goal of HbA1c<7% was 50.8 %. Patients with adequate glycaemic control had more acceptable BMI than those with inadequate glycaemic control. In patients not achieving a goal of HbA1c < 7%, higher level of plasma glucose and total cholesterol was determined compared to those with adequate glycaemic control. There were no significant differences in the HDL-C, triglycerides or albumin:creatinine ratios in patients with both adequate and inadequate glycaemic control.*

key words: *type 2 diabetes, sulfonylurea, hypoglycemia*

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Background and aims

Diabetes mellitus (DM) is a major cause of morbidity and premature mortality with microvascular and macrovascular complications and increased health-care resource use [1]. Up to 27% of all deaths worldwide in the age group of 35–64 years might be attributed to diabetes mellitus [2], in a setting where the International Diabetes Federation Atlas (2017) quotes 57 million Europeans as having diabetes, with the prevalence projected to reach 71 million by 2040. Tight glycaemic control can reduce the risk of type 2 diabetes complications [3]. In 2017 IDF Diabetes Atlas estimated that there are currently 1.785 million people living with DM in Romania. National prevalence of DM was estimated by Guariguata et al. [4] to be 5.1% for 2013 in Romania, with increasing predictions to 6.4% in 2035. In 2010, data from the National Program for Diabetes showed that 803 489 patients were registered as beneficiaries, equivalent to a prevalence of 4.2% [5]. According to the 2017 IDF Diabetes Atlas for Romania, a national prevalence of DM was 9.7% estimated while a European average is 6.8%. The results of the most recent published study [6] showed a prevalence of known DM of 9.2%, which is similar to the estimate presented in IDF Diabetes Atlas for 2017.

The main objectives for the treatment type 2 diabetes are to prevent or delay complications, while preserving the quality of life. Attainment is possible by management of glycemic control and cardiovascular risk factors during regular follow-up visits, while ar the same time enhancing the patient-centered approach in order to involve the individual`s engagement in self-care activities [7]. According to international guidelines metformin is recommended as first antihyperglycemic agent in addition to diet and exercise, if tolerated and not contraindicated. Sulphonylureas (SUs) are recommended as a second step besides other alternative oral antihyperglycemic agents [8]. Based on guideline recommendations, long term experience and low treatment costs, both drug classes are the most frequently prescribed oral antihyperglycemic agents globally. Hypoglycemia is a clinically important adverse health outcome associated with SU therapy. Hypoglycemia is recognized to have a detrimental clinical effect, in terms of mortality, morbidity, adherence to therapy, and quality of life [9-13]. Hypoglycemia is highly prevalent in patients with type 2 diabetes mellitus (T2DM) treated with antihyperglycemic medications. In the RECAP-DM Asia Pacific (AP) and RECAP DM European Union (EU) studies, symptoms of hypoglycemia were reported to be ~36% of treated patients in the AP region and ~38% of treated patients in the EU region [14,15]. The RECAP studies were among first large scale observational studies to report the prevalence of hypoglycemia in a real world setting. In Romania there is no information about real life prevalence of hypoglycemia in SU treated patients. Therefore, the primary objective of this study was to assess the prevalence of hypoglycemia in SU (as monotherapy or in combination with metformin) treated T2DM patients in Romania. Secondary objectives was to assess the proportion of T2DM patients in Romania treated with SUs (as monotherapy or in combination with metformin) who are not at the HbA1c goal of <7% and the extent to which more hypoglycemia frequency and severity is associated with lower treatment adherence, lower treatment satisfaction, lower quality of life and more worry/fear of hypoglycemia.

Material and method

Methods

This was a multi-center, observational study using retrospective clinical chart and laboratory parameters review, and a cross-sectional survey in Romania. Potential study subjects were T2DM patients who were scheduled for a routine office visit. During the routine office visit, the patients' eligibility was assessed by the physician reviewing the patient clinical charts to ensure that all inclusion and no exclusion criteria were met (ADA/EASD consensus).

Eligible patients included in the study provided a signed informed consent form and completed a series of questionnaires comprising of data on patient reported hypoglycemia experience (including frequency/severity), adherence, quality of life (QoL), treatment satisfaction, fear of hypoglycemia, weight gain and lifestyle/behavioral factors. Hospital/local ethical review boards approved the informed consent document and the study protocol. In addition, all participating physicians completed a questionnaire collecting data on patients age, gender, setting, specialty, type of practice and years of experience, treatment priorities, decision making behaviors, knowledge about guidelines, and treatment goals. Inclusion criteria were that patients had to be diagnosed with T2DM based on ADA criteria, and were at least 30 years of age at time of T2DM diagnosis. Also, only patients who have been taking SU (monotherapy or in combination therapy with metformin) for at least 6 months prior to enrollment were included. Patient's medical records include a minimum core data set.

Exclusion criteria implies patients with type 1 DM, pregnant women / or with gestational DM,

patients who have been taking DPP4 inhibitors, GLP-1 Receptor agonists, SGLT 2 inhibitors, α glucosidase inhibitors, meglitinides, PPAR-gamma agonists or insulin during the 6 months prior to enrollment, and those who were already participating in a clinical trial or other clinical study.

Variables and Epidemiological Measurements

The study population consisted of 385 adult patients diagnosed with T2DM according to ADA criteria, with age of 30 years or older and who had been undergoing treatment with SU (monotherapy or in combination therapy with metformin) for at least 6 months. Total study duration was 2 months. Descriptive analyses were performed for summarizing socio-demographic, clinical and lifestyle/behavioural variables of study patients. Data on hypoglycaemia and weight gain were summarized using descriptive statistics. The prevalence of inadequate glycaemic control in real-life was determined by computing the percentage of patients not achieving HbA1c target level recommended by local/international guidelines. Socio-demographic and clinical variables were compared between patients with inadequate and adequate control using corresponding bivariate tests. Impacts of hypoglycaemia (stratified by frequency and severity) and weight gain on patient-reported outcomes including adherence, quality of life (QoL), treatment satisfaction, and fear of hypoglycaemia were evaluated using corresponding bivariate tests which are added in Annex. This study was observational in nature. Hence, no treatment assignment or randomization was used.

Statistical analysis

The prevalence of hypoglycaemia was calculated as the ratio of subjects with self-reported or documented (in patient medical chart) hypoglycaemia in all SU (as monotherapy or in combination with metformin) treated

T2DM patients. The association between hypoglycaemia frequency, severity and lower treatment adherence, lower treatment satisfaction, lower quality of life and increased worry/fear of hypoglycaemia was investigated by calculating the correlation coefficient between each pair of factors using Spearman's rho or Pearson's r, as appropriate. Factors significantly ($p<0.05$) associated with adherence, quality of life (QoL), treatment satisfaction, and fear of hypoglycaemia in bivariate analyses were further assessed using multivariate analyses. Statistical analysis was performed using SPSS 19.0.

Results

Total patient population included in the study was 385 patients, of whom 42.2% had experienced hypoglycaemia in the previous 6 months. Only 18% of all patients enrolled in the study received SU monotherapy, namely patients received gliclazide (77%) followed by glimepiride (13%) and gliquidone (10%). Among the 314 patients (82%) on dual therapy the most common dual therapy prescribed was gliclazide+metformin (77%), followed by glimepiride+metformin (14%), gliquidone+metformin (1%) and glibenclamide+metformin (8%). No meaningful differences in demographic (age and gender) or anthropometric (body weight and height) characteristics of patients were observed. Patient characteristics are presented in Table 1.

Table 1. Patient's characteristics enrolled in the study

Characteristics		All patients (n=385)
Age (mean ± s.d.)		65.37±8.90
Female sex		51.8%
Marital status	Single	4.2%
	Married	74.1%
	Divorced	5.0%
	Widowed	16.6%
Education	Elementary education	38.4%
	Secondary	45.0%
	College	15.0%
	Postgraduate	1.6%
Height, cm (mean ± s.d.)		1.66±0.09
Weight, kg (mean ± s.d.)		83.57±13.86
BMI (kg/m^2)		30.44±4.38
underweight	<18.5	0.3%
normal	≥18.5 to <25	8.4%
overweight	≥25 to <30	40.1%
obese I	≥30 to <35	36.9%
obese II	≥35	14.4%
Diabetes duration (years)		7.76±5.71
Age at diagnosis		57.75±9.46
Smoking		10.5%
Alcohol consumption	Never	41.4%
	Occasionally / at weekends	50.8%
	Daily	2.4%
	Unknown	5.5%
Follow low sugar diet		89.9%
Follow low calorie diet		41.4%
Physical activity once a week or more		45.8%
Experienced side effects		20.9%
Prevalence of hypoglycaemia		42.2%
Glycaemic control HbA1c (mean % ± s.d.)		7.12±1.06
HbA1c ≥ 7		49.2%
HbA1c < 7		50.8%

From the questionnaire it can be concluded that patients were not on low fat diet and preferred low sugar diet. When asked about their health, generally, most of them did not have problems with mobility, self-care and usual activities. They denied experiencing pain, anxiety or depression and were satisfied with treatment and/or mitigation of symptoms by use of medication. The amount of time that took the medication to start working did not present a problem. Generally, 79% of patients did not experience any side effects. In patients who did experience side effects, 73% of them did not found side effects bothersome. The experienced side effects did not interfere with their health and mental function. Ease of use with the treatment regime was acceptable to 88% patients. Strict every day adherence to therapy was 77%. Percentage of patients who followed specific diabetes diet were 71.3%, but only 28% exercised regularly. Patients enrolled in the

study did not fear consequences of hypoglycemia. In the last year, the weight was stable for the majority of participants. Even if patients gained weight, it was modest gain less than 5 kilograms.

Primary outcome

Prevalence of Hypoglycaemia

Of the 385 study patients 3 of them (0.8%) had no data recorded regarding hypoglycaemia symptoms. Among the remaining 382 patients the prevalence of hypoglycaemia in the past 6 months was 42.2%. The prevalence of mild symptoms was 32.5%, moderate was 13.9%, severe was 3.7% and the prevalence of very severe symptoms was 0.8%. The prevalence of hypoglycaemia (Table 2) was highest in the 50-60 age category, and lowest among the eldest subjects (70 years and above).

The prevalence of hypoglycaemia was highest in the Glibenclamide group, 62.5%; and lowest in the Gliquidone group, 11.1%. (Table 3).

Table 2. Prevalence of hypoglycaemia by age category

Have you ever felt symptoms of low blood sugar in the last 6 months?	Age category				Total
	< 50	50 to 60	60 to 70	≥ 70	
	Yes				
	42.1%	49.2%	42.1%	38.6%	42.2%
	No				
	57.9%	50.8%	57.9%	61.4%	57.8%

Table 3. Prevalence of hypoglycaemia by sulphonylurea type

Have you ever felt symptoms of low blood sugar in the last 6 months?	Sulphonylurea type				Total
	Gliclazide	Glimepiride	Gliquidone	Glibenclamide	
	Yes				
	40,3%	49,1%	11,1%	62,5%	42,2%
	No				
	59,7%	50,9%	88,9%	37,5%	57,8%

Secondary outcomes

HbA1c was recorded for 238 subjects with mean of 7.12 (4.8-10.97) %. Mean fasting plasma glucose value was 148.39 (77.00-355.00) mg/dl while total cholesterol level was recorded with a mean of 183.63 (97-409) mg/dl. HDL-cholesterol level was 48.45 (21-168) mg/dl and LDL-cholesterol level was at 101.39 (20.6-181)/dl. Triglyceride level had a mean value of 179.16 (55-1199) mg/dl and albumin:creatinine ratio was recorded with a mean value of 24.60 (0.64 - 168) mg/dl. Waist circumference was 100.40 (59-137) cm. The mean systolic blood pressure was 138.11(104-210) mmHg while the mean diastolic blood pressure was 79.20 (30-150) mmHg. Out of the 238 patients with available HbA1c value 50.8% were at the target goal of HbA1c<7%. There was no difference in the age, gender, nor weight distribution of patients with adequate and inadequate glycaemic control. Patients with adequate glycaemic control have significantly lower BMI than those with inadequate glycaemic control. There was no difference in the diabetes duration, in the alcohol consumption and smoking habits pattern nor in the age at diagnosis of those patients. Patients

who did not reach the target goal of HbA1c < 7% implicitly had a higher level of the plasma glucose than those with adequate glycemic control, 164.76±40.8 compared to 136.28±32.53 mg/dl, respectively. Patients with inadequate glycaemic control presented a higher level of total cholesterol. There were no significant differences in the HDL-C, triglycerides and albumin:creatinine ratios in patients with adequate and inadequate glycaemic control. The waist circumference was similar in both groups.

Association of hypoglycaemia with self-reported outcomes

No difference in treatment adherence of patients reporting hypoglycaemia episodes and those not reporting was observed. Patients who reported hypoglycaemia episodes in the last 6 months were satisfied with the overall treatment and their overall health status score was satisfactory. Fear of experiencing hypoglycaemic episodes is shown in Table 4 and was significantly different ($p<0.001$) in patients experiencing hypoglycaemic episodes within last 6 months compared to those not experiencing hypoglycaemia. Overall, patients who have not experienced hypoglycaemic episodes during last 6 months were less afraid of repeating the episode.

Stepwise regression was performed for assessing the association between hypoglycaemic episodes and the self-reported outcomes found to be significantly correlated in the univariate analyses. Four of the hypoglycaemia worry questionnaire scores were included in the final model after performing the stepwise regression: Q1, Q8, Q13 and Q17 (Table 4). All four questions were found to be significant, the first three of them decreasing while the last increasing the probability of having a hypoglycaemic episode. Fear of not recognizing hypoglycaemia was associated with 18% decrease in chance of having a hypoglycaemic episode in patients who did not experience hypoglycaemia within last 6 months. Fear of not having someone to help during hypoglycaemia was associated with 15% decrease, while feeling of lightheaded/dizziness was associated with 12% decrease in chance of having a hypoglycaemic episode in patients who did not experience hypoglycaemia within last 6 months. Fear of developing hypoglycaemia was associated with 9% increase in chance of having a hypoglycaemic episode in patients who did not experience hypoglycaemia within last 6 months.

Table 4. Fear of experiencing hypoglycaemic episodes in patients from Romania.

Because my blood sugar could go low, I worried about	Experienced hypoglycaemia symptoms* (n=159)					No hypoglycaemia symptoms* (n=219)					p value
	Never	Rarely	Sometimes	Often	Almost always	Never	Rarely	Sometimes	Often	Almost always	
1. not recognizing it	37.7%	30.8%	25.8%	5.7%	0.0%	83.6%	14.2%	1.8%	0.0%	0.5%	<0.001
2. not having sugary drinks or foods available	49.1%	23.3%	23.9%	3.1%	0.6%	87.2%	11.0%	1.8%	0.0%	0.0%	<0.001
3. passing out in public	52.5%	26.7%	15.8%	5.1%	0.0%	88.6%	9.1%	1.4%	0.9%	0.0	<0.001
4. embarrassing myself or my friends in public	55.7%	25.9%	15.8%	2.5%	0.0%	92.7%	6.4%	0.9%	0.0%	0.0%	<0.001
5. having a hypoglycaemic episode while alone	45.9%	28.9%	18.9%	5.7%	0.6%	83.1%	12.8%	3.7%	0.0%	0.5%	<0.001

Table 4. *Continued.*

Because my blood sugar could go low, I worried about	Experienced hypoglycaemia symptoms* (n=159)					No hypoglycaemia symptoms* (n=219)					p value
	Never	Rarely	Sometimes	Often	Almost always	Never	Rarely	Sometimes	Often	Almost always	
6. appearing stupid or drunk	62.3%	18.9%	15.7%	1.9%	1.3%	90.9%	7.8%	0.9%	0.5%	0.0%	<0.001
7. losing control	52.8%	27.0%	15.7%	1.9%	2.5%	88.5%	9.6%	1.8%	0.0%	0.0%	<0.001
8. no one helping during hypoglycaemia	47.5%	22.8%	22.2%	5.1%	2.5%	87.2%	11.0%	1.4%	0.5%	0.0%	<0.001
9. having hypoglycaemia while driving	68.8%	16.9%	11.7%	2.6%	0.0%	91.3%	7.8%	0.9%	0.0%	0.0%	<0.001
10. making a mistake or having an accident	62.0%	20.9%	12.7%	2.5%	1.9%	92.7%	6.4%	0.0%	0.5%	0.0%	<0.001
11. getting a bad evaluation or being criticized	61.4%	21.5%	13.9%	1.9%	1.3%	95.4%	3.7%	0.5%	0.5%	0.0%	<0.001
12. difficulty thinking clearly when responsible for others	52.5%	26.7%	15.8%	3.2%	1.9%	91.8%	6.4%	1.4%	0.0%	0.5%	<0.001
13. feeling lightheaded or dizzy	43.7%	35.4%	17.7%	1.9%	1.3%	85.3%	13.3%	1.4%	0.0%	0.0%	<0.001
14. accidentally injuring myself or others	52.8%	27.7%	15.1%	2.5%	1.9%	86.8%	10.5%	2.3%	0.5%	0.0%	<0.001
15. permanent injury or damage to my health	55.7%	24.7%	12.7%	2.5%	4.4%	91.8%	5.5%	1.8%	0.5%	0.5%	<0.001
16. low blood sugar interfering with activity	50.0%	25.9%	18.4%	4.4%	1.3%	91.8%	5.9%	1.8%	0.5%	0.0%	<0.001
17. becoming hypoglycemic during sleep	49.7%	27.0%	15.1%	4.4%	3.8%	84.0%	11.4%	3.7%	0.0%	0.9%	<0.001
18. becoming emotionally upset and difficult to deal with	54.7%	25.2%	15.1%	3.1%	1.9%	88.6%	9.1%	0.5%	0.5%	1.4%	<0.001

* within last 6 months

Discussion

In the sample of 385 type 2 diabetes patients treated with either SU monotherapy or SU and metformin combination, prevalence of hypoglycaemia was 42.2 % in the 6 months prior to the study. Patients experiencing hypoglycaemic symptoms within last 6 months had a higher degree of fear/worry about hypoglycaemia.

Hypoglycaemia prevalence in Romania was the 3rd highest prevalence rate in Europe with respect to the current published data. Based on findings from three large randomized controlled trials (ACCORD, ADVANCE, VADT) [16-18] the clinical relevance of hypoglycemic events has become increasingly important in international guidelines for the treatment of T2DM reported in the previous RECAP studies conducted in Asia and Europe [14,15]. The prevalence in those studies ranged between approximately 0.25 and 0.50 (country specific prevalences were as follows: UK 0.536, Spain 0.37, France 0.387, Norway 0.354, France 0.481, Germany 0.242, Poland 0.329, China 0.417, Korea 0.39, Malaysia 0.33, and Taiwan 0.294*).*

Without the active and lasting participation of the patient no medication, no matter how effective can attain good glycemic control [19]. Quality of life for T2DM patients is dominantly

conditioned by frequency of hypoglycemia. According to the UGDP study, frequency of severe hypoglycemic episodes is 10% and light episodes is 40%. In our study the prevalence of hypoglycaemia was highest in the Glibenclamide group, 62.5%; and lowest in the Gliquidone group, 11.1% which represent 8% and 1% of study participants.

Patient-centered outcomes such as treatment satisfaction and preference are increasingly being recognized as mediators of health-prone behaviours, such as long-term persistence with treatment regimens. Our study was aimed at surveying how patients' reports of hypoglycaemic symptoms were associated with their treatment satisfaction and adherence. There was no was no difference in treatment adherence of patients reporting hypoglycaemia episodes and those not reporting. However, there was a significant difference in overall treatment satisfaction of patients reporting hypoglycaemia episodes and those not reporting.

Our results of self-reported hypoglycaemic episodes (41.6%) are in line with previous findings from a Scandinavian group which has shown that the incidence of self-reported hypoglycaemia was 37% in a study of 399 outpatients with T2DM receiving oral antihyperglycaemic treatment and/or insulin [11]. Also, Alvarez Guisasola et al. [15] in their study on 1709 T2DM patients have shown a self-reported value for hypoglycaemia of 38.4%. In Asian RECAP-DM study self-reported hypoglycaemia symptoms were somewhat lower at 35.8% in 2257 patients with T2DM.

As a result, the adverse events experienced with SUs might make treatment unappealing for most patients and adherence may be low, making early T2DM patients difficult to treat effectively. There is a clear need for therapeutic options with good efficacy and an improved safety and tolerability profile which are likely to confer significant advantage in terms of patient adherence, especially in early stages or in newly diagnosed patients. In addition to the problem of non-adherence due to undesirable adverse events, there is also the perception that adherence is inversely related to the frequency of dosing. From this perspective, the administration of some pharmacological treatments in mono-therapy for T2DM should be relatively effective in terms of compliance. However, given that many patients with T2DM will progress to combination therapies as insulin secretion deteriorates as the disease progresses, treatment regimens increase in complexity and adherence becomes an even bigger issue. New products with simpler dosing regimen, both in mono and in combination therapies, may help to address the adherence issue [20].

Limitations of this study may impair the generalization and reliability of its conclusions. First, this was an observational study using retrospective clinical chart and laboratory parameters review in a selected group of patients. Therefore, they may not be representative of the general population of patients with T2DM, especially taking into consideration that mean age of patients was 65 years. Other potential limitations include dependence on self-report to evaluate both medication adherence and the occurrence of hypoglycaemic symptoms because self-reported hypoglycaemia may not be reliable. Patients usually overestimate medication adherence and underestimate hypoglycaemic episodes by failing to recognize nocturnal episodes. More objective measures, particularly self-monitoring of blood glucose, might be useful in confirming the present findings. Given the observational (non-interventional) nature of our study and its reliance on self-report, causality cannot be determined. For instance, it is possible that patients who were generally more satisfied with

their treatments might have been more likely to adhere and less likely to recall and/or report symptoms of hypoglycaemia.

Finally, patients were recruited by using a sample of physicians who had agreed to participate in the study.

Conclusions

The prevalence of hypoglycaemia in the past 6 months was 42.2% being highest in the 50-60 age category and lowest among the eldest subjects. Prevalence of patients at the target goal of HbA1c<7% was 50.8 %. Patients who did not reach the target of HbA1c < 7% had implicitly higher level of the plasma glucose and level of total cholesterol than those with adequate glycaemic control. Patients who reported hypoglycaemia episodes in last 6 months were satisfied with the overall treatment and their overall health status score was satisfactory. From Hypoglycaemia Worry questionnaire, "Fear of not recognizing hypoglycaemia; Fear of not having someone to help during hypoglycaemia; Fear of feeling lightheaded/dizziness" were associated with a decrease in the chance of having a hypoglycaemic episode in patients who did not experience hypoglycaemia. The opposite was associated with "Fear of becoming hypoglycaemic", namely an increase in the chance of having a hypoglycaemic episode in patients who did not experience hypoglycaemia. In conclusion, fear of experiencing hypoglycaemic episodes was lower in patients not experiencing hypoglycaemia. Overall, patients who did not experience hypoglycaemic episodes were less afraid of repeating the episode.

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