Improving Therapeutic Adherence of Oral Antidiabetics in Insulin-Dependent Patients with Type 2 Diabetes Mellitus: the Combination of a Fixed-Dose

Márquez-Rivero S1, Márquez-Contreras E2, López-García-Ramos L2, Castaño-Durán C1, Marcos-Sánchez A1, Pérez-Espinosa JR1, Ortega-Navarro P1, Weber-Fernández AM1, Gil-Cañete A1 and Gil-Guillén V1

1Compliance and Inertia Working Group, Spanish Society of Hypertension (SEH-LELHA), Unidad de Gestión Clínica El Molino de la Vega, Huelva, Spain
2Compliance and Inertia Working Group, Spanish Society of Hypertension (SEH-LELHA), Unidad de Gestión Clínica San Juan del Puerto, Spain
3Compliance and Inertia Working Group, Spanish Society of Hypertension (SEH-LELHA), Universidad de Medicina, Alicante, Spain

*Corresponding author: Emilio Márquez-Contreras, Compliance and Inertia Working Group, Spanish Society of Hypertension (SEH-LELHA), Unidad de Gestión Clínica El Molino de la Vega, C/Puerto 7, 6º D. Huelva-21003, Spain

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Abstract

Objective: To assess whether the combination of fixed-dose Oral Antidiabetic drugs (OA) in a single tablet compared to OA separated into 2 or more tablets is an effective strategy to improve adherence in insulin-dependent patients with Type 2 Diabetes Mellitus (DM2).

Methods: This was a prospective, longitudinal, multi-center study, carried out in 3 primary care centers in Spain. One hundred and twenty patients treated with OA and insulin prescribed for insulin-dependent DM2 were included. A cluster randomization was performed based on two groups: (1) Control Group (CG): Sixty patients treated with two OA prescribed separately in different tablets, and (2) an Intervention Group (IG): Sixty patients treated with OA were with 2 drugs in combination at a fixed dose, in a single tablet. Three visits took place. AO Adherence was measured by using electronic monitors (MEMS). Average adherence percentage (%; Average AP) and daily compliance (%; Daily AP) was calculated. A patient was considered adherent when AP was 80–100%. Insulin adherence was measured by counting.

Results: One hundred and ten patients completed the study (79 in the IG and 31 in the CG). Global adherence was 92.59% and 79.62% in IG and 82.85% and 48.21% in CG at 6 and 12 months, respectively (p<0.05 by groups). Daily adherence was 79.62% and 62.96% in IG and 17.85% and 10.71% in CG at 6 and 12 months, respectively (p<0.05). Global adherence with insulin by count was 77.78% and 70.37% in IG and 57.14% and 60.71% in CG at 6 and 12 months, respectively with significant differences. In the non-adherent group, the number of concomitant medications and glucemia and haemoglobin A glycosylate levels at 6 and 12 months, were significantly higher than in the adherent population. The NNT was 4.42 patients to prevent one non-adherence.

Conclusions: The combination of fixed-dose OA in a single tablet compared to OA separated into 2 or more tablets is an effective strategy to improve AO therapeutic adherence in patients with insulin-dependent DM2.

Keywords: Therapeutic adherence; Oral antidiabetic drugs; Insulin; Insulin-dependent type 2 diabetes

Introduction

Type 2 Diabetes Mellitus (DM2) is a highly prevalent, chronic metabolic disease with tremendous public health and socioeconomic implications. The International Diabetes Federation estimates suggest that there are more than a half-billion adults ages 20 years to 79 years worldwide who have DM2 and that the global health care expenditure for adults with DM2 in 2015 was $673 billion [1] and has a significant social, emotional, and behavioral impact on the lives of patients [2].

It is known that many patients with DM2 are not achieving optimal glucose control [1]. There is strong evidence that improved glycemic control (lowering Glycated Hemoglobin A1C (HbA1c) to ≤7%) can reduce the risk of microvascular and macrovascular complications.

An important barrier to achieving optimal metabolic control is non-adherence to recommended lifestyle changes and/or prescribed medication regimens.

Adherence to medication imposes important therapeutic and economic implications in diabetics [3]. Drug adherence is defined as the extent to which patients take the medication being prescribed by their health care provider [4].

Non-adherence to prescribed DM2 medications are, however, common and remain a barrier to optimal health outcomes [1-5]. A meta-analysis of 27 studies of adherence rates to DM2 medications found that only 22% of studies reported greater than or equal to 80% adherence among patients [6]. Krass et al in a review of 27 studies observed that the prevalence of adherence ranged from 38.5 to 93.1% [7]. Non-adherence with OA in Spain ranges between 45 and 51.5% [8-10] and with insulin it is 25.25% [11].

Non-adherence is associated with an increase in morbidity and mortality in DM2 [1,12,13]. Such reduced adherence not only
results in poor health outcomes but it also has a significant impact on healthcare costs and significantly affects the quality of life in DM2 patients [14]. Thus, the overall management of DM2 should address adherence as well as appropriate medications.

To improve patient management and overall adherence to OA, it is essential to identify factors that account for non-adherence and define intervention strategies [15]. Studies that analyze interventions to improve therapeutic adherence with OA in insulin-dependent patients with DM2 are scarce. Measures to increase patient satisfaction and counteract a lack of adherence must be multifactorial; strategies should include a reduction in the complexity of the prescription regimen, educational initiatives, improved doctor–patient communication, reminder systems and reduced costs.

Currently, there are a number of fixed-dose combinations of agents for the treatment of hyperglycemia in DM2, which simplify administration regimens and increase patient adherence compared with equivalent combinations of separate tablets [12,16,17].

Our goals were to assess whether the combination of fixed-dose Oral Antidiabetic drugs (OA) in a single tablet compared to OA separated into 2 or more tablets is an effective strategy to improve adherence in insulin-dependent patients with DM2 and to identify different non-adherence patterns, as well as endpoints and causes related to non-adherence.

Materials and Methods

Design and setting

The Diabet-Cumple study was a multicentric, prospective, observational study carried out in 3 primary care centers in Spain, between June 2019 and December 2020. Fifteen investigators enrolled 120 consecutive patients with a diagnosis of DM2 (each of which included 8 patients). The study duration was 18 months.

Inclusion criteria

Patients were included if the following inclusion criteria were met: 1.- Patients to whom the use of OA for insulin-dependent DM2 was indicated, previously known and recorded in clinical history; 3.- Patients older than 45 years; 4.- Patients should be treated with OA and insulin at least 2 months continuously before their inclusion in the study. The patient had to have prescribed 2 different OA (prescribed in a fixed combination or separately depending on the intervention or control group and one of them was metformin, being the second or third ADO at the discretion of the investigator) and each of them could be taking between 1 and 3 daily doses; 5.- Patients who gave their informed written consent.

Exclusion criteria

Patients were excluded if the following exclusion criteria were met: 1.- Patients with a pathological situation that may interfere with medication intake (e.g. acute stroke or acute myocardial infarction); 2.- Pregnant or breastfeeding women; 3.- Patients who had cohabitants taking the same OA or insulin; 4.- Patients participating in other research studies.

Criteria for withdrawal from the study

Patients could be withdrawn from the study when the treating physician considered an increase of more than 30% of the visits originally programmed in the study. Patients who lost or did not use the Medication Event Monitoring System (MEMS) and those who decided not to continue with the study at some point were also withdrawn.

Study schedule

The planned study schedule consisted of 3 visits: the inclusion visit (baseline) plus 2 follow-up visits after 6 and 12 months. Adherence to pharmacologic treatment was measured using MEMS [18]. MEMS are electronic monitoring devices that have a digital recording device in the form of a microchip in the lid of the drug container that automatically controls its opening and registers the time and date of the opening. Adherence to insulin was measured by counting insulin.

During the inclusion and follow-up visits, blood pressure, lipid parameters, glycaemia, glycated hemoglobin levels, GFR and weight were recorded. In the final visit, the MEMS were returned to the treating physicians.

Study groups

Investigators were cluster-randomized to a Control Group (CG) or an Intervention Group (IG). Patients were assigned according to the group to which each investigator was assigned. The randomization process was centralized and blind, performed using random number tables and by a person not involved in the follow-up.

The groups that were created were: 1.- Control Group (CG): 60 patients, who received the intervention that their family doctor usually applies in the management of the insulin-dependent diabetic patient in consult and were treated with two OA prescribed separately in different tablets. One of the two AO was always metformin, the other ADO was prescribed according to the usual practice of the family doctor. 2.- Intervention group (IG): 60 patients who received a similar intervention, but the treatment with OA was with 2 drugs in combination at a fixed dose, in a single tablet. One of the two AO was always metformin, the other ADO was prescribed according to the usual practice of the family doctor.

Endpoints

The average Adherence Percentage (AP) was calculated using the following formula:

\[
\text{Mean AP} = \frac{(\text{Total number of tablets assumed to have been taken/Total number of tablets that should have been taken}) \times 100}{1}
\]

The average AP was calculated as:

1.- Global percentage of doses taken (global AP) (all doses taken in an established period).
2.- Percentage of correct days (daily AP); Percentage of days on which OAC was taken correctly (2 daily intakes).
3.- Percentage of correct time (time AP); Percentage of patients taking the medication at the prescribed time (Breakfast between 7 and 9 o’clock in the morning (a.m.), lunch between 13:30 and 15:30 and dinner between 20.30 and 22.30 hours in the evening (p.m)).
4.- Percentage of therapeutic cover: AP of therapeutic
Adherence was defined as:

1. Global adherence: Global AP between 80 and 100%.
2. Daily adherence: Daily AP between 80 and 100%.
3. Correct time adherence: Time AP between 80 and 100%.

Endpoints

| Endpoints                          | Intervention Group N = 54 | Control Group N = 56 | p-value* | Adherent Group N = 79 | Non Adherent Group N= 31 | p-value** |
|------------------------------------|---------------------------|----------------------|----------|------------------------|--------------------------|-----------|
| Sex:                              |                           |                      |          |                        |                          |           |
| Women: n (%)                       | 26 (48,15 %)              | 27 (48,21 %)         | 0.12     | 44 (55,70 %)           | 18 (58,06 %)              | 0.16      |
| Men: n (%)                         | 28 (51,85 %)              | 29 (51,79 %)         |          | 35 (44,30 %)           | 13 (41,94 %)              |           |
| Age (years, mean (SD))            | 68,22 (SD 7,4)            | 68,5 (SD 8)          | 0.11     | 67,62 (SD 8,7)         | 70,35 (SD 8,6)            | >0.1      |
| Current diseases (mean(SD))       | 7,46 (SD 2,7)             | 7,55 (SD 2,7)        | 0.1      | 7,20 (SD 2,9)          | 8,32 (SD 1,95)            | 0.21      |
| Concomitant medication(mean (SD)) | 8,33 (SD 3,26)            | 8,39 (SD 3,5)        | <0.05    | 7,84 (SD 2,97)         | 9,67 (SD 3)               | <0.01     |

Exploratory parameters

| Endpoint                           | Mean (SD) | Mean (SD) | p-value |
|------------------------------------|-----------|-----------|---------|
| Baseline systolic blood pressure (SBP) (mmHg) | 133,1 (SD16) | 134,37 (SD 8) | 0.21 |
| 6-month SBP (mmHg)                 | 104,81 (SD 54) | 125,14 (SD 35) | <0.05 |
| 12-month SBP (mmHg)                | 129,05 (SD 11) | 131,58 (SD 19) | <0.05 |
| Baseline Diastolic Blood Pressure (DBP) (mmHg) | 76,22 (SD 8) | 77,15 (SD 6) | 0.12 |
| 6-month DBP (mmHg)                 | 66,55 (SD 31) | 71,16 (SD 20) | <0.05 |
| 12-month DBP (mmHg)                | 73,68 (SD 11) | 75,13 (SD 11) | 0.18 |
| Baseline body-weight (Kg.)         | 77,4 (SD13) | 75,89 (SD 8) | 0.22 |
| 6-month body-weight (Kg.)          | 76,85 (SD 11) | 75,05 (SD 8) | 0.11 |
| 12-month body-weight (Kg.)         | 77,72 (SD 13) | 75,91 (SD 9) | 0.08 |

Analytical parameters

| Endpoint                           | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
|------------------------------------|-----------|-----------|-----------|-----------|
| Baseline Total Cholesterol (mg/dl) | 127,26 (SD 19) | 129,76 (SD 34) | 198,78 (SD 24) | 205,19 (SD 29) |
| 6-month Total Cholesterol (mg/dl)  | 120,82 (SD 25) | 121,07 (SD 26) | 198,68 (SD 28) | 205,19 (SD 32) |
| 12-month Total Cholesterol (mg/dl) | 125,45 (SD 57) | 126,58 (SD 42) | 197,28 (SD 27) | 205,19 (SD 32) |
| Baseline Total triglycerids (mg/dl) | 119,34 (SD 65) | 120,78 (SD 39) | 183,07 (SD 28) | 205,19 (SD 32) |
| 6-month Total triglycerids (mg/dl) | 127,76 (SD60) | 129,47 (SD 39) | 183,07 (SD 28) | 205,19 (SD 32) |
| Baseline HDL cholesterol (mg/dl)   | 50,93 (SD9,6) | 51,43 (SD8,4) | 51,57 (SD 9) | 51,43 (SD8,4) |
| 6-month HDL colesterol (mg/dl)     | 52,06 (SD9,6) | 53,98 (SD7,1) | 53,5 (SD 8) | 53,98 (SD7,1) |
| 12-month HDL colesterol (mg/dl)    | 51,86 (SD 9) | 53,66 (SD9) | 53,4 (SD 8) | 53,66 (SD9) |
| Baseline LDL cholesterol (mg/dl)   | 119,25 (SD 33) | 127,26 (SD 30) | 189,68 (SD 28) | 205,19 (SD 32) |
| 6-month LDL cholesterol (mg/dl)    | 110,82 (SD 25) | 121,07 (SD 26) | 198,06 (SD 32) | 205,19 (SD 32) |
| 12-month LDL cholesterol (mg/dl)   | 104,49 (SD 25) | 116,09 (SD 30) | 205,77 (SD 32) | 205,19 (SD 32) |
| Baseline Glomerular Filtration rate (mg/dl/1.73 m²) | 87,7 (SD 21) | 87,25 (SD 18) | 124,3 (SD 57) | 198,68 (SD 28) |
| 6-month Glomerular Filtration rate (mg/dl/1.73 m²) | 86,76 (SD 19) | 86,29 (SD14) | 128,63 (SD 53) | 205,19 (SD 32) |
| 12-month Glomerular Filtration rate (mg/dl/1.73 m²) | 84,91 (SD 16) | 84,51 (SD 14) | 125,72 (SD 38) | 205,19 (SD 32) |
| Baseline Glycaemia                 | 171,46 (SD 43) | 184,35 (SD 35) | 172,68 (SD 41) | 198,68 (SD 28) |
| 6-month Glycaemia                  | 150,03 (SD 31) | 162,03 (SD 30) | 156,98 (SD 37) | 198,68 (SD 28) |
| 12-month Glycaemia                 | 148,83 (SD 27) | 177,03 (SD25) | 151,49 (SD 37) | 198,68 (SD 28) |
| Baseline Glycated hemoglobin       | 7,67 (SD0,87) | 7,68 (SD 1,14) | 7,62 (SD1,12) | 124,3 (SD 57) |
| 6-month Glycated hemoglobin        | 7,43 (SD 0,4) | 7,84 (SD 0,4) | 7,42 (SD 0,5) | 124,3 (SD 57) |
| 12-month Glycated hemoglobin       | 7,29 (SD 0,49) | 7,83 (SD 0,43) | 7,37 (SD0,58) | 124,3 (SD 57) |

N=simple size, %=percentage, NS= Non significant. Results expressed in means and Standard Deviation (SD) or number of patients and percentage. p: statistically significant differences in the decreases between the beginning and the end of the study by intervention groups (p-value*) and by adherents and non-adherents group (p-value**).

Coverage assuming a 12-hour therapeutic effect of AO.

1. Global adherence: Global AP between 80 and 100%.
2. Daily adherence: Daily AP between 80 and 100%.
3. Correct time adherence: Time AP between 80 and 100%.
4. Therapeutic cover adherence: Therapeutic cover AP between 80 and 100%.

Overall good adherence was considered with values in a range between 80-100%. The main endpoint was the global adherence (the efficacy of the investigated interventions was measured by this
Different non-adherence patterns were defined [18] according to AP as:

- Adherents: a) Absolute adherent with AP of 100%, b) Masked adherent with AP >80% and daily AP of <80%, c) Adherent with sporadic non-adherence when AP >80% and less than 100%, and d) Over-adherence with AP >100%.

- Non-adherents: a) Absolute non-adherence when AP <50%, b) Partial non-compliance when AP between 50% and 80%, and c) Treatment abandonment when the patient stopped taking the medication (as declared by the patient and as recorded in MEMS).

Other patterns (Adherent or non-adherent): a) Forecasted non-adherence after presenting a fixed pattern of non-adherence, b) Pharmacologic vacations of at least 3 days without taking the medication, c) White coat compliance when the medication was taken the days before and after the visit, with non-adherence the rest of the time, d) Schedule/time non-adherence when the medication was not taken as prescribed. Mixed non-adherence was defined when 2 or more non-adherence patterns were met.

**Calculation of the Sample Size**

Based on the recommendations for studies that obtain means as the principal results and require analyses using bilateral comparisons, and considering the observation of differences of 25% in the mean AP between the two groups to be clinically relevant (Adherence expected in the control arm was 65%), the following formula was used: N = \left( \frac{Z_{\alpha}^2 \cdot p \cdot (1-p) + Z_{\beta}^2 \cdot p_1 \cdot (1-p_1) + p_2 \cdot (1-p_2)}{(p_1-p_2)^2} \right) where “n” is the number of individuals required per group; Zα ¼ 0.05, corresponding to a value of 1.96; Zβ= 5% = 1.645. We added a 12% to face possible loss, summing up a total of 120 patients. After the calculations, we found a sample size of 60 patients to be included in each study group. The parameters used in the sample calculation are based on data obtained in the bibliography [18].

**Statistical analysis**

The Student’s t test, the McNemar and test chi-squared test were used for the comparison of quantitative and qualitative endpoints for paired and unpaired data. It was considered significant a p<0.05 and Confidence Intervals (CI) were of 95%. Data of compliance is showed with and 70,37% in IG and 57,14% and 60,71% in CG at 6 and 12 months, respectively. The AP distribution was not taken as prescribed. Mixed non-adherence was defined when 2 or more non-adherence patterns were met.

**Results**

A total of 120 patients with insulin-dependent DM2 were included, and 110 completed the study, with adherence data on all of them. Fifty-three patients were women (50.6%) and 57 were men (49.6%) (p>0.05 by sex). Average age was 68,39 years (Standard Deviation (SD) 7,8) in the overall population (68,2 years [SD 7.9] for men and 68,58 [SD 7,8] for women; p>0.05 by sex). Ten patients were withdrawn from the study due to: loss, malfunction or rupture of the MEMS (n=2), lost to follow-up (n=6), or address change (n=2). Of the 10 patients that withdrew from the study, 6 belonged to the IG and 4 belonged to CG; with similar withdrawal causes in both groups. There was no significant difference in the baseline characteristics of the patients who completed the study compared with those who withdrew from the study.

Global adherence with OA in the sample (n=79) was 93,63%, 65,45% and 71,81% at 6, 12 months and globally respectively. Daily adherence was 49,09%, 36,36% and 40% at 6, 12 months and globally respectively.

Global adherence with insulin by count was 60,90%, with no significant differences between 0-6 months and 6-12 months (67,27% and 64,54%).

59,10% were adherents with OA and insulin, 26,26% were non-adherents with both, 12,71% were OA adherent and insulin non-adherent, and 1.82% were insulin adherent and ADO non-adherent.

There were 54 evaluable patients in IG (49,1 of 110 patients) and 56 in CG. General data, exploratory and analytical parameters by intervention group and by adherents and non-adherents groups at baseline, 6 and 12 months are detailed in Table 1. Significant differences were observed between groups (IG-CG and adherents–non-adherents) in several endpoints. The Systolic Blood Pressure (SBP) values at 6 and 12 months and Diastolic Blood Pressure (DBP) at 12 months were significantly higher in CG compared with IG. Glucemia and HbA1c levels at 6 and 12 months were lower in IG compared with CG. In the non-adherent population, the number of concomitant medications, SBP and DBP values at baseline and at 12 months, weight, total cholesterol, and LDL cholesterol at baseline, 6 and 12 months and glucemia and HbA1c levels at 6 and 12 months, were significantly higher than in the adherent population. No differences were observed in the cardiovascular risk factors analyzed.

Global adherence in the sample was 92,59% and 79,62% in IG and 82,85% and 48,21% in CG at 6 and 12 months, respectively (p<0.05 by groups).

Daily adherence was 79,62% and 62,96% in IG and 17,85% and 10,71% in CG at 6 and 12 months, respectively. The AP distribution and adherence by study groups are shown in Table 2 (p<0.05 by groups).

Global adherence in the sample with insulin by count was 77,78% and 70,37% in IG and 57,14% and 60,71% in CG at 6 and 12 months.
Table 2: Adherence percentages, according to different ways to comply and percentage of adherence by intervention groups.

| Intervention Group N = 54 | Control Group N = 56 | p-value |
|---------------------------|----------------------|---------|
|                           | 6 Months             | 12 Months| 6 Months             | 12 Months |
| Percentage doses taken    | 90.16% (82.26-98.06) | 85.80% (76.94-94.9) | 86.07% (77.91-95.13) | 77.94% (67.08-88.8) | <0.05 | <0.05 |
| Global adherence          | 92.59% (85.61-99.57) | 79.82% (68.88-90.36) | 82.85% (76.11-89.24) | 48.21% (35.13-61.29) | <0.05 | <0.001 |
| Percentage of correct days| 82.78% (72.78-92.78) | 75.85% (66.45-87.25) | 75.39% (64.11-86.67) | 62.62% (49.95-75.29) | <0.01 | <0.01 |
| Daily adherence           | 79.62% (69.88-90.36) | 62.96% (50.08-75.84) | 17.85% (7.83-27.87) | 10.71% (2.62-18.8) | <0.001 | <0.001 |
| Percentage of correct time| 71.17% (59.09-83.25) | 66.59% (54.01-79.17) | 66.29% (53.91-78.67) | 55.34% (42.32-68.36) | <0.01 | <0.01 |
| Correct time adherence    | 25.92% (14.24-37.6)  | 22.22% (11.36-33.08) | 7.14% (0.44-13.84) | 5.35% (0.27-10.43) | <0.001 | <0.001 |
| Percentage of therapeutic cover | 92.35% (85.35-99.35) | 88.85% (80.46-97.24) | 89.70% (81.89-97.6) | 85.68% (76.51-94.85) | <0.05 | NS |
| Therapeutic cover adherence| 92.59% (85.61-99.57) | 92.59% (85.61-99.57) | 98.21% (94.81-100) | 80.35% (69.95-90.75) | <0.05 | <0.05 |

Results expressed in percentage and confidence intervals. p-value: Statistically significant differences in the decreases between the beginning and six months (p’), and twelve months (p”), by groups.

Table 3: Different adherence patterns.

| Pattern Description | Percentage |
|---------------------|------------|
| A) Adherent         | 71.81% (N= 79) |
| • Absolute adherent  | 2.72% (IC= 0-6.2%) |
| • Masked adherent    | 3.72% (IC= 22.38-43.06%) |
| • Adherent with sporadic non-adherence. | 35.46% (IC= 24.96-45.96%) |
| • Over adherence.    | 0.91% (IC= 0-2.91%) |
| B) Non-Adherent      | 28.19% (N= 31) |
| • Absolute non-adherent. | 1.82% (IC= 0-6.5%) |
| • Partial non-adherent. | 25.46% (IC=10.13-40.79 %) |
| • Treatment abandoned. | 0.91% (IC= 0-4.21%) |
| C) Other Patterns    |          |
| • Estimated non-adherence (> or < 80%) | 3.63% (IC=0.23-7.03%) |
| • Pharmacological holidays (> or < 80%) | 6.36% (IC=1.86-10.86%) |
| • White robe adherence (>80%) | 4.94% (IC= 0.74-8.34%) |
| • Non-adherence of intake. | 80.91% (IC=73.61-88.21%) |
| • Mixed non-adherence (> or < 80%) | 45.45% (IC=36.15-54.75%) |

Data in % (CI); CI= confidence limit at 95%.

Discussion

The Diabet-Cumple study assessed adherence to OA in standard clinical practice conditions and is the first study that assesses the efficacy of a fixed-dose combination of OA intervention, as a strategy to improve adherence in patients with insulin-dependent DM2, prescribed according to the Standards of Medical Care in Diabetes (ADA 2019) guide for the treatment of DM2 [19].

Global adherence was significantly higher in IG than in CG at 6 and 12 (92.59% vs 79.62% and 82.85% and 48.21%, respectively). Differences greater than 30% have been observed between both groups at 12 months, demonstrating the effectiveness of the intervention. Daily adherence was 79.62% and 62.62% in IG vs 17.85% and 10.71% in CG at 6 and 12 months, respectively. The Global adherence with insulin was significantly higher on the GI. The clinical relevance of this intervention is important as it obtained an ARR at the end of the intervention of 22.62%, a RRR of 57.77% and a NNT of 4.42 patients.

The ARR at the end of the intervention was 22.62%. The RRR was 57.77% and the NNT was 4.42 patients.

In the logistical regression stepwise multivariable analysis, there was significant association (p<0.05) with non-adherence for the number concomitant medications (odds ratio OR 0.31), baseline SBP (OR 0.28), baseline DBP (OR 0.26), baseline weight (OR 0.28), baseline total cholesterol (OR 0.19), LDL cholesterol (OR 0.18), glycaemia (OR 0.34) and Hba1c (OR 0.36). We included endpoints that, although not significant, could have had relevance from a clinical perspective (age, sex, etc). The resulting model was significant (p<0.05) and the classification percentage was 73%.

Different adherence patterns that were observed are presented in Table 3 and Table 4.

The ARR at the end of the intervention was 22.62%. The RRR was 57.77% and the NNT was 4.42 patients.
Significant differences between both groups are observed in glycemia and glycosylated hemoglobin obtained at 6 and 12 months, with higher values in the CG. The HBG was 7.67 at baseline, 7.43 at 6 months and 7.29 at 12 months in the IG and 7.68, 7.84 and 7.83 in the CG. Blood glucose levels were 171.46, 150.03, and 148.83 in the IG and 184.35, 182.03, and 177.03 in the CG, respectively. In this way, the efficacy of the intervention is demonstrated, favoring adherence with OA and insulin and with a favorable effect on disease control indicator parameters.

Significant differences were observed in the percentage of adherence between 6 and 12 months overall, with a higher percentage at 6 months. The Hawtorse effect probably influenced these findings. Global adherence was 71.81% at the end of the study, Daily adherence 40%, and Correct time adherence was 19%. These results reflect the difficulties of taking a medication in real life, with greater difficulty if it is daily, and even more if it has to be taken at a specific time. A high percentage of compliers was obtained in the time of therapeutic cover adherence, probably due to the use of 2 daily doses in many of them.

It has been observed that the percentage of non-adherence was higher with insulin than with OA, with 12.71% being OA adherent and insulin non-adherent. Likewise, it was observed that 59.10% were adherent with OA and insulin, 26.26% non-adherent with both, and 1.82% adherent with insulin and non-adherent with OA.

The percentage of adherence observed in our study is similar to others, within the variability of non-adherence presented by the different national studies [8-11] or international studies [1,5-7,20-23].

60.90% were adherent to insulin, observing that more than a third of insulin-dependent diabetics do not take more than 20% of the insulin prescribed daily. These results are superior to other studies [24,25] and inferior to others with 74.75% [11] and even others where greater adherence was obtained with slow insulin compared to rapid insulin [13].

In a systematic review that included 70 studies, Hutchins V et al. [17] observed that the fixed combination of OA drugs improved adherence by 10-13% compared to the free combination. It was observed that the change from monotherapy to fixed combination decreased adherence by 1.5% and when switching to free combination it decreased by 10%. Consequently, the greater number of drugs is associated with greater adherence to treatment with OAD.

In the non-adherent population, the number of concomitant medications, SBP and DBP values at baseline and at 12 months, weight, total cholesterol, and LDL cholesterol at baseline, 6 and 12 months and glycaemia and HbA1c levels at 6 and 12 months, were significantly higher than in the adherent population. Similarly, significant differences were observed in blood glucose and glycosylated hemoglobin values between those who complied with and who did not comply with insulin treatment.

In the logistical regression multivariable analysis, an association between these endpoints and non-adherence was detected, and a very significant model (p<0.001) was obtained, with a 73% of adherence classification. The number of drugs consumed, SBP, DBP, weight, total cholesterol, LDL-C and initial blood glucose levels could be markers of a higher percentage of non-adherence.

Other studies have obtained similar data [26] to Diabet-Cumple study. Other related factors have been costly and complicated dosing regimens, patients’ misconceptions about the initiation of insulin therapy [20,27-29], use of rapid insulin [24], advanced age, white race, lack of alcohol consumption, and taking less than 3 OA drugs daily [30].

Different OA treatment adherence patterns were studied with MEMS, with similar results as in other studies [18-26]. Among all patterns, the sporadic non-adherence and masked adherent pattern and the partial non-adherent pattern stand out. What is also remarkable is the high percentage of patients with a pattern of schedule/time non-adherence. The pattern of over-adherence was almost non-existent.

The results of this study can be generalized to a specific type of patient, very common in clinical practice. These would be patients treated with metformin two OA prescribed separately in different tablets or 2 OA drugs in combination at a fixed who attend primary care. The results are strengthened because of the sufficient sample size, were obtained through consecutive sampling, and with a relevant number of investigators from primary healthcare centers across Spain. Furthermore, the study fulfills the criteria recommended by Haynes et al. for adherence studies [31]. An assessment of the adherence results show a follow-up of at least 80% of a sample of at least 50 individuals [31] and the MEMS, considered a gold standard in adherence investigations. These were used as the method to measure OA therapeutic adherence [33,34]. For our team, the preferable method to measure adherence is the use of MEMS. It is a method with greater validation and the experience of our team is high.

As for limitations of the study, MEMS is the most recommended method to measure adherence [32,33] although it was initially noted that it improves adherence (Hawthorne effect) by 6%, the effects decline over time. Fortunately, overestimation was 1.12%. For this reason it does not affect the results significantly. The clinical use of MEMS is limited by its high cost and the 3-year duration of the battery; hence it is mainly used in research, or in non-adherent patients, when aiming to promote treatment adherence. Also, patients with insufficient adherence data (10 patients) might have slightly influenced the results, although an analysis of non-evaluable patients showed similar baseline characteristics as the patients that were evaluated. However, such limitations are assumed as normal in observational studies on health effectiveness in clinical practice and in clinical effectiveness.

Data on OA and insulin adherence in a real-world setting are needed to provide a more reliable estimate of medication adherence rates. As a line of future research we recommend studies designed to seek easy and cheap strategies that improve the therapeutic adherence with OA and insulin in the short- and long-term and studies designed to assess adherence in insulin-dependent DM2 with validated measurement methods such as the count, pharmacy databases, MEMS or electronic prescription [34-36], avoiding those with less validation [35,36].

**Conclusion**

We can conclude that the combination of fixed-dose Oral Antidiabetic drugs (OA) in a single tablet compared to OA separated
into 2 or more tablets is an effective strategy to improve therapeutic adherence in insulin-dependent patients with DM2. The percentages of those who comply with the prescribed daily doses and those who comply with the recommended schedule are especially low and unexpected.

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