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A quantitative assessment of patient barriers to insulin

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Disclosures
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SUMMARY

Aim: To assess diabetes treatment preferences with a focus on patient barriers to insulin treatment. **Materials and Methods:** A questionnaire using indirect and direct methods was administered as part of the International Diabetes Management Practices Study (IDMPS). Discrete choice modelling was used to assess how product attributes influence patients' preferences for diabetes treatment. A multinomial logit model was used to find the odds ratio for each parameter, representing the probability of selecting a chosen alternative given a choice set. This allowed for the derivation of relative attribute importance, an indication of how influential product attributes are in the respondents' choices. **Results:** The IDMPS questionnaire was administered to 14,033 individuals with diabetes in 18 countries. The majority of respondents were women (53%) and had Type 2 diabetes mellitus (T2DM; 85%). Across subgroups, administration (i.e. oral vs. injection) was a driver of preference. Patient preferences varied according to diabetes type; individuals with T2DM assigned much higher relative importance to administration than those with Type 1 diabetes mellitus (T1DM; 30.86% vs. 4.99%; $p < 0.0001$). Individuals with T2DM treated with insulin placed less importance on administration than insulin-naïve T2DM patients (3.09% vs. 47.48%; $p < 0.0001$). Diabetes education also had a significant effect on the priority given to administration between T2DM patients who received diabetes training and those who did not (28.21% vs. 33.68%, respectively; $p < 0.0001$). **Conclusion:** The insulin barriers perceived by patients with diabetes evolved with their disease experience. While administration was the primary preference driver for insulin-naïve patients, patients were increasingly concerned with more clinically relevant barriers as they gained experience with insulin. This finding suggests that patients using insulin understand the importance of achieving an optimal balance between safety and efficacy.

What's known
The epidemiology and treatment options for both Type 1 and Type 2 diabetes are well understood. Insulin is used to treat T1DM and can be part of the treatment regimen for T2DM. This integral therapy is administered either by pump or subcutaneously through a syringe or an insulin pen.

What's new
This paper elucidates the drivers and patient preferences regarding insulin therapy in Africa/Middle East, Asia, Eastern Europe and Latin America. This study found that barriers to insulin treatment evolved with the patients' disease experiences; insulin-naïve patients were most concerned with administration form and those experienced with insulin were primarily concerned with clinically relevant barriers.

Introduction

Type 1 diabetes mellitus (T1DM) is a disease in which the destruction of pancreatic β-cells usually results in no endogenous insulin production (1). This disease typically develops in children, teens and young adults, though it can also present later in life (2). Type 2 diabetes mellitus (T2DM) appears when the β-cell function cannot efficiently manage the increased peripheral demand of insulin (3). While this type tends to affect adults, there is an increasing incidence of T2DM in children (4). T2DM is largely associated with excess body weight and physical inactivity; it is responsible for 90% of diabetes cases worldwide (5). Common consequences of diabetes include increased risk of heart disease and stroke, diabetic retinopathy, kidney failure and diabetic neuropathy (4). The International Diabetes Federation estimates that 285 million adults (ages 20–79) worldwide will have diabetes in 2010 (6) with an uneven geographic distribution: 3.2% of adults in Africa, 7.7% of adults in the Middle East and North Africa, 6.3% of adults in South and Central America, 7.0% of adults in South-East Asia, 7.1% of adults in India, 5.0% of adults in the Western Pacific and 11.7% of adults in North America and the Caribbean will have diabetes (7–13).

Numerous alternatives are currently available for diabetes treatment; T1DM patients are treated with insulin, which can be administered through a pump or subcutaneously through a syringe or an insulin pen. T1DM patients may also receive pramlintide injections in addition to insulin. Pramlintide is a synthetic analogue of amylin, which is a hormone normally co-released with insulin that aids in the control of blood glucose levels (14). For T2DM, the American

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Diabetes Association and the European Association for the Study of Diabetes recommend metformin coupled with life-style changes as a first-line treatment (15). When this regime fails to achieve treatment goals, other oral drugs can be added, namely sulfonylureas, alpha-glucosidase inhibitors, thiazolidinedione, exenatide and glinidines. Two new drug categories, glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 inhibitors, show promise in improving upon current therapeutic offerings for T2DM. Insulin, either alone or in combination with oral drugs (usually metformin), is also used for the treatment of individuals with T2DM (4).

Despite the different mechanisms of action and administration forms of these compounds, their use in daily practice is affected by doctor and patient preferences. Discrete Choice Modeling (DCM, aka Choice-based Conjoint), a market research method which utilises known multivariate modelling techniques to determine the importance of product attributes, can be used to assess the impact of these variables on drug selection and use. While many questionnaires ask respondents direct questions, DCM questionnaires aim to indirectly determine how product attributes influence patients' preferences by simulating realistic decision scenarios. The goal of this approach is to understand the trade-offs consumers make when selecting a product over a competitor.

While the diabetes pathogenesis, consequences and treatment effects are relatively well understood, there is a lack of knowledge regarding the drivers of patient preferences and their perceptions of diabetes treatment alternatives. Thus, the main objective of this study was to use DCM to identify patient preferences and perceptions of diabetes therapies, with a focus on identifying patient barriers to insulin use.

Methods

Study design and data source

The International Diabetes Management Practices Study (IDMPS) is an international, multicentre, observational study of individuals with T1DM or T2DM. Patients from the IDMPS registry completed a 15-min questionnaire, which included both direct and indirect discrete choice scenario questions requiring patients to consider criteria in order to make a choice between two treatment options.

Study population

The IDMPS study population included patients from Africa/Middle East (Algeria, Egypt, Iran, Lebanon, Morocco, Tunisia, Saudi Arabia and the United Arab Emirates), Asia (China, Malaysia and Thailand), Eastern Europe (Turkey) and Latin America (Argentina, Chile, Colombia, Guatemala, Mexico and Venezuela). Patients were included in the IDMPS provided that they: (i) were ≥ 18 years of age, (ii) had diagnosed T1DM or T2DM and (iii) provided written informed consent. Criteria for patient exclusion were: (i) concomitant participation in another clinical study, (ii) participation in a previous IDMPS wave and (iii) current temporary insulin treatment. The patient questionnaires used for the analysis were completed in 2008.

Methods

Discrete Choice Modeling was employed to indirectly determine how product attributes influence patients' preferences for diabetes treatment. For this purpose, treatment attributes and their corresponding levels were identified and translated into hypothetical scenarios within choice sets for inclusion in the patient questionnaire (Table 1). This questionnaire was then fielded via the IDMPS. A multinomial logit model was then used to analyse the DCM data and compute the odds ratio for each parameter (corresponding to the studied attributes). The multinomial logit model examined the probability of selecting a chosen alternative given a choice set, and the model output allowed for the derivation of the relative attribute importance, which demonstrates how influential product attributes (e.g. administration, dosing, etc.) are in the respondents' decisions. Relative attribute importance (which indicates the attributes' impact on patient preferences) was derived using the relative magnitudes of the parameter estimates associated with each attribute. Interaction terms between attributes and subgroups were included in the models, and the statistical significance of these interactions served to provide comparisons of the differences in attribute importance between the subgroups.

Institutional Review Board/Ethics Committee approval was not required for this study.

Statistical analysis

Direct and indirect questions were included in the questionnaire. For direct questions, frequencies (numbers and proportions) and distributions (mean, standard deviation, median and range) were examined for categorical and continuous measures, respectively.

Results

Study population

The IDMPS questionnaire was administered to 14,033 diabetes patients in 18 countries. The majority of the respondents came from Latin America and

Table 1 Therapy attributes: the treatment attributes assessed were administration, dosing, maintenance of blood sugar, risk of hypoglycemia and presence of side effects

Attributes	Levels
Administration	1. Oral
	2. Injection
Dosing	1. Once daily
	2. Twice daily
	3. Three or more times daily
Maintenance of blood sugar	1. Maintains good blood sugar levels MOST of the time
	2. Maintains good blood sugar levels SOME of the time
	3. Maintains good blood sugar RARELY
Risk of hypoglycaemia symptoms	1. High risk of symptoms from low blood sugar (from sweating and lightheaded to seizure, loss of consciousness)
	2. Low risk of symptoms from low blood sugar (from sweating and lightheaded to seizure, loss of consciousness)
	3. No risk of symptoms from low blood sugar
Presence of side effects	1. Some chance of mild non-threatening side effects (e.g. rash)
	2. Some chance of bothersome non-life threatening side effects (e.g. GI/abdominal pain)
	3. Some chances of serious side effects (e.g. cardiac issues)

Africa/Middle East, were women (53%) and had T2DM (85%). The mean age of the population was 54 years. More than half (56%) of the respondents reported receiving diabetes education and 48% of patients were self-monitoring their blood glucose levels (Table 2).

Relative attribute importance

Ten choice sets, with two scenarios in each one, were included in the DCM section of the questionnaire. Examining model results for the full study population revealed that many of the attributes hold a similar level of importance. However, sub-analyses revealed a much greater variation in relative attribute importance between various subpopulations. Across subgroups, the difference between oral and injectable administration is a primary driver of patient preference, while risk of hypoglycaemia symptoms did not heavily influence treatment decisions. Patient preferences varied significantly according to diabetes type, with T2DM patients assigning much higher relative importance to administration than T1DM patients (30.86% vs. 4.99%, respectively; $p < 0.0001$; Figure 1). T1DM patients were most concerned with possible side effects and maintenance of blood glucose levels (35.72% and 28.80%, respectively; $p < 0.0001$; Figure 1). Experience with insulin treatment also had a significant impact on the importance placed on administration, with insulin-treated T2DM patients placing less importance on oral vs. injection administration than insulin-naïve T2DM patients (3.09% vs. 47.48%, respectively; $p < 0.0001$; Figure 2). Furthermore, patients treated with insulin assign greater importance to side effects compared to insulin-naïve patients (31.59% vs. 13.75%, respectively; $p < 0.0001$; Figure 2). Diabetes education also had a significant effect on the importance assigned to administration between T2DM patients who received diabetes training and those who did not (28.21% vs. 33.68%, respectively; $p < 0.0001$; Figure 3).

An analysis of relative attribute importance by region revealed interesting findings regarding the difference in priority given to certain attributes. Similar importance was assigned to administration, ranging from 19.61% in Latin America to 28.92% in Eastern Europe ($p < 0.0001$; Figure 4). Latin America's attribute importance ratings were the most dissimilar among the regions examined. While Eastern Europe, Africa/Middle East and Asia ascribed the greatest relative importance to the presence of side effects (37.56%, 32.05% and 29.63%, respectively), Latin America considered side effects to be the second least important attribute (13.77%; $p < 0.0001$). Africa/Middle East, Asia and Eastern Europe assigned low importance to risk of hypoglycaemia (14.00%, 8.75% and 8.20%, respectively), while Latin America placed the greatest importance on this attribute (28.21%; $p < 0.0001$). The regions also varied in the relative importance they assigned to maintenance of blood glucose levels, ranging from Eastern Europe assigning it as the second least important (12.17%) and Latin America assigning it as the second most important (27.30%; $p < 0.0001$). All regions attributed similar levels of importance to dosing, ranging from 10.18% in Africa/Middle East to 13.15% in Eastern Europe ($p < 0.0001$; Figure 4).

Table 2 Patient demographics: the majority of the respondents came from Latin America and Africa/Middle East, were female and had T2DM

	Patients *N* (%)
Mean age (SD)	54 (15)
Gender	
Male	6325 (45)
Female	7371 (53)
Frequency missing	337 (2)
Region	
Africa/Middle East	4402 (31)
Algeria	455 (3)
Egypt	423 (3)
Lebanon	533 (4)
Morocco	704 (5)
Iran	1077 (8)
Tunisia	474 (3)
Saudi Arabia	306 (2)
United Arab Emirates	430 (3)
Asia	1752 (12)
China	636 (5)
Malaysia	590 (4)
Thailand	526 (4)
Eastern Europe	1334 (10)
Turkey	1334 (10)
Latin America	6545 (47)
Argentina	851 (6)
Chile	755 (5)
Colombia	879 (6)
Guatemala	588 (4)
Mexico	2781 (20)
Venezuela	691 (5)
Frequency missing	0 (0)
Type of diabetes	
Type 1	2144 (15)
Type 2	11,883 (85)
Frequency missing	6 (∼0)
Self-monitor blood glucose levels	
Yes	6794 (48)
No	6981 (50)
Unknown	258 (2)
Health insurance coverage	
Public	7023 (50)
Private	2337 (17)
Public + private	1010 (7)
None	3280 (23)
Unknown	312 (2)
Level of education	
University/Higher Education	3634 (26)
Primary/Secondary Education	8390 (60)
Illiterate	1236 (9)
Frequency missing	773 (6)
Diabetes training	
Yes	7841 (56)
No	5741 (41)
Unknown	437 (3)
Frequency missing	14 (∼0)
T2DM demographics	
Region	
Africa/Middle East	3583 (30)
Asia	1543 (13)
Eastern Europe	1088 (9)
Latin America	5669 (48)
Frequency missing	0 (0)
Diabetes training	
Yes	6339 (53)
No	5165 (43)
Unknown	365 (3)
Frequency missing	14 (∼0)
Insulin treatment	
Yes	3747 (32)
No	7751 (65)
Frequency missing	385 (3)

Discussion

The comparison of sub-populations showed that patients preferred to be treated with oral rather than with injectable drugs. This finding is well aligned with other similar studies comparing injectable with inhaled insulin preferences (16). They also indicate that individuals with T2DM assign greater importance to treatment administration when compared to other attributes such as side effects; these data coincide with the results of the 2005 patient-preference study comparing insulin administration (17). Conversely, individuals with T1DM placed higher priority on avoiding adverse side effects and maintaining blood glucose control. Similar uneven priorities were observed when comparing insulin-naïve patients vs. those treated with insulin. The differences in priorities between individuals with T1DM and T2DM suggest that, in addition to greater experience with insulin therapy, the experience gained in disease control itself may also play a role in determining such preferences. It is also noteworthy that within the T2DM group, patients who had undergone diabetes training placed lower priority on the administration of product.

Limitations

Several limitations may affect the validity of the study outcomes. Our patient population was defined by the IDMPS inclusion/exclusion criteria and consequently, it is not necessarily identical to that of the real-world population. This fact limits the generalisability of the study conclusions. However, the study population comes from 18 countries, thus providing

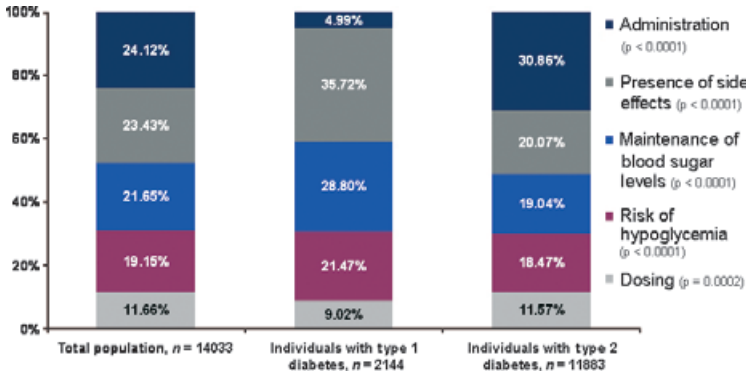

Figure 1 Comparison of relative attribute importance for individuals with different types of diabetes. Study results indicate a significant difference in relative attribute importance between T1DM and T2DM individuals

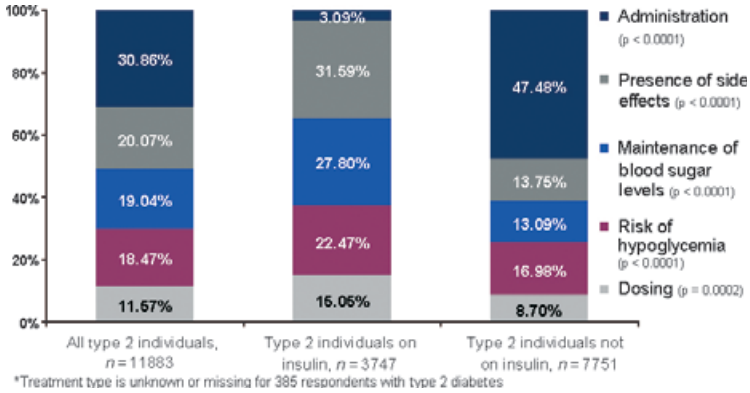

Figure 2 Comparison of relative attribute importance for Type 2 diabetes individuals by insulin use*. When comparing T2DM patients who are treated with insulin to those treated without insulin, there are significant differences in relative attribute importance ratings

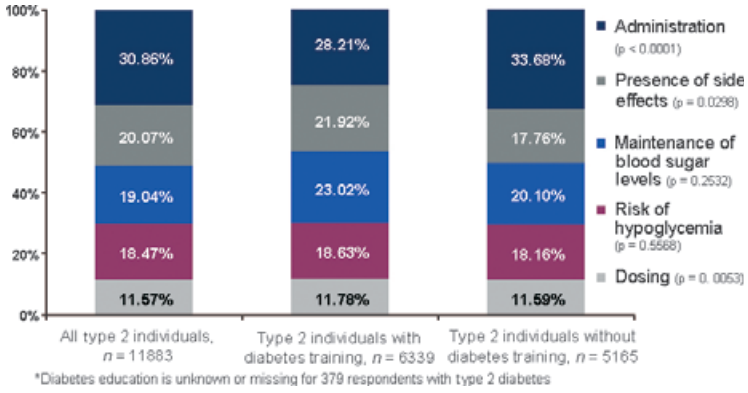

Figure 3 Comparison of relative attribute importance for Type 2 diabetes individuals with varying levels of diabetes training*. Study findings demonstrate that diabetes education had a significant effect on the importance assigned to administration for T2DM individuals

both regional and cultural diversity that could not be achieved easily in a single-country study.

It is important to note that the questionnaire focused on insulin therapy only, and did not contain questions regarding GLP-1 receptor agonists such as exenatide and liraglutide. However, as these agents are only approved for the treatment of type T2DM (18), their inclusion in the questionnaire would

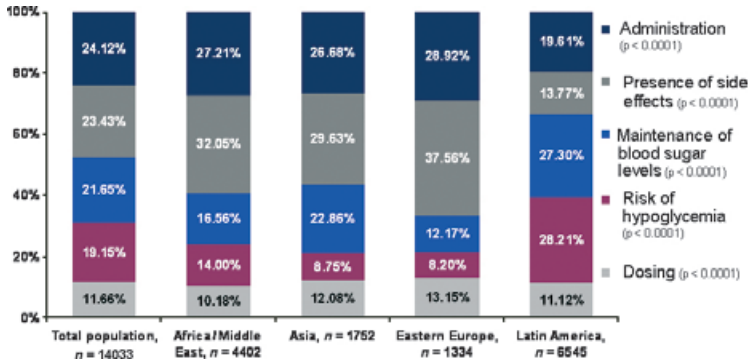

Figure 4 Comparison of relative attribute importance by geographic region. When comparing attribute importance ratings between regions, a number of significant similarities and differences exist between the different locales

presumably have impacted the responses of T2DM patients only. Also, these GLP-1 receptor agonists are administered through subcutaneous injection (18), and are not available in an oral form. Therefore, it is unlikely that questions regarding these agents would have had an appreciable impact on responses related to oral vs. injectable formulation.

The results obtained in this study could be distorted by response bias, whereby survey responders feel obligated to answer questions in a manner that would please the study sponsor. Furthermore, all study analyses were based on observational data, and therefore only information collected at the time of study was available for analysis.

Although DCM is a validated research method for eliciting patient preferences, there are limitations inherent to this type of analysis. Ideally, the experimental design would include choice sets encompassing all possible scenario with minimal overlap, balance in attribute level occurrence within the choice sets and orthogonality (i.e. not confounding) (19). However, in a real-world setting, respondent fatigue limits the practicality of testing the ideal number of scenario. In order to address this limitation, statistical software [SAS version 9.1 (20)] was used to identify efficient experimental designs with combinations of choice sets aimed at maintaining a balanced and orthogonal design without causing respondent fatigue.

Additionally, DCM assumes compensatory decision-making among patients (19), i.e. the methodology assumes that survey participants are able to consider all attributes when they provide their responses. While a lack of compensatory decision-making may affect the accuracy of the results, its magnitude cannot be measured.

Although DCM is a useful technique for examining patient treatment preferences, further research is needed to refine the methodology as a means of comparing differences in relative attribute importance between subgroups (19,21). As there is currently no standard methodology for making these comparisons, examination of the statistical significance of interaction terms between treatment attributes and subgroups served to approximate the statistical differences.

Conclusion

The results of this study suggest that individuals' perceived barriers to insulin therapy are significantly influenced by factors such as: (i) the experience acquired with insulin treatment, self-metabolic control and negative side effects of its administration; and (ii) the diabetes education received. This concept is supported by the finding that insulin-naïve patients report greater levels of concern with the type of treatment administration while those who have experience with disease control and insulin therapy placed greater priority on clinically relevant attributes such as control of blood glucose levels and side effects. This trend towards de-emphasis on the importance of administration is also observed in individuals with T2DM who have received diabetes education. These findings underscore the value of providing education regarding treatment options for patients with diabetes, as the perceived ideal treatment may change over the course of the disease experience and may vary according to geographical location.

Author contributions

Roman Casciano contributed to developing the concept and design of the study, the analysis of the data, and drafting and critically revising the paper. He approves of the paper. Elisabetta Malangone contributed to the concept and design of the study, data analysis and interpretation, and drafting and critical

revision of the paper. She approves of the paper. Ambady Ramachandran contributed to the acquisition of the data and drafting and critical revision of the paper. He approves of the paper. Juan Jose Gagliardino contributed to the acquisition of the data and drafting and critical revision of the paper. He approves of the paper.

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