FEATURE ARTICLE

Exploring Why People With Type 2 Diabetes Do or Do Not Persist With Glucagon-Like Peptide-1 Receptor Agonist Therapy: A Qualitative Study

William Polonsky,[1] Cory Gamble,[2] Neeraj Iyer,[2] Mona Martin,[3] and Carol Hamersky[2]

[1]Behavioral Diabetes Institute, San Diego, CA; [2]Novo Nordisk, Plainsboro, NJ; [3]Health Research Associates, Inc., Mountlake Terrace, WA

OBJECTIVE | Despite the demonstrated benefits of glucagon-like peptide 1 (GLP-1) receptor agonist therapy, adherence and persistence with this therapy is often challenging. The purpose of this study was to expand current understanding of patients' experiences, motivations, and challenges relevant to their persistence with GLP-1 receptor agonist therapy.

DESIGN AND METHODS | This noninterventional, cross-sectional, qualitative study used face-to-face interviews with 36 adults with type 2 diabetes who had been treated with at least one GLP-1 receptor agonist medication. Inclusion criteria were: ≥18 years of age, diagnosed with type 2 diabetes, and currently treated with a GLP-1 receptor agonist for ≥1 month at the time of screening ("continuers") or discontinued use of a GLP-1 receptor agonist ≤1 year of screening but with a total ≥1 month of treatment ("discontinuers"). Interviews were conducted using a semi-structured qualitative interview guide that included open-ended questions and probes to obtain both spontaneous and prompted input from participants about their current and past treatment experiences with GLP-1 receptor agonist therapy.

RESULTS | Among continuers (n = 16), the most commonly identified facilitators supporting the decision to continue were the observations of improved glucose control (50%) and weight loss (55%). Among discontinuers (n = 20), the most commonly identified challenges leading to treatment discontinuation were side effects (55%) and high cost (50%). Continuers were more likely than discontinuers to receive clinically relevant information from their health care team, including facts about GLP-1 receptor agonist medications, likely treatment benefits, the importance of gradual dose titration, and the need to adjust diet after initiation.

CONCLUSION | Although cost is a major obstacle to treatment continuation, it can only be resolved through changes in ongoing reimbursement coverage and policies. However, many other obstacles could potentially be addressed (e.g., reducing side effects with gradual dosage titration and setting appropriate expectations regarding efficacy) through more collaborative patient-clinician interactions before initiating therapy.

Glucagon-like peptide 1 (GLP-1) receptor agonists are an innovative class of medications for people with type 2 diabetes that enhances glucose-dependent insulin secretion, suppresses pancreatic glucagon production, slows gastric motility, and reduces body weight by increasing satiety and decreasing appetite (1,2). Importantly, treatment with a GLP-1 receptor agonist confers a low risk of hypoglycemia when given as monotherapy or in the absence of sulfonylureas or insulin (2), and recent studies have linked certain GLP-1 receptor agonist formulations with cardiovascular (3–5) and renal (3,4,6,7) benefits, as well as cost savings (8–10).

Individuals who persist with GLP-1 receptor agonist therapy achieve significant A1C reductions, are more likely to achieve an A1C of <7%, and experience fewer hospitalizations and shorter hospital stays (8–10). As recently reported by Shah et al. (10), in individuals with type 2 diabetes and established cardiovascular disease (CVD) or elevated cardiovascular risk, treatment with a GLP-1 receptor agonist (liraglutide) was found to be a cost-effective and budget-neutral option with U.S. managed care plans. Recent guidelines from the American Diabetes Association recommend that a GLP-1 receptor agonist should be considered when atherosclerotic CVD, heart failure, or chronic kidney disease predominates, independent of A1C (11).

Despite the demonstrated benefits of GLP-1 receptor agonist therapy, adherence and persistence with therapy is

Corresponding author: Carol Hamersky, cahy@novonordisk.com

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frequently problematic, and discontinuation rates are high (12). As reported by Alatorre et al. (13), the proportion of people with type 2 diabetes who discontinued treatment during the first 6 months can range from 26 to 48%, depending on the formulation and/or required injection frequency (e.g., twice daily, once daily, or once weekly) (14). In a recent survey of 2,173 individuals with type 2 diabetes who discontinued GLP-1 receptor agonist therapy, respondents identified gastrointestinal side effects ("made me feel sick," 64.4%; "made me throw up," 45.4%) as their primary reason for discontinuation. Other reasons included "a preference for oral medications" (39.7%) and "inadequate blood glucose control" (34.5%) (15).

Although use of once-weekly formulations (e.g., semaglutide, extended-release exenatide, and dulaglutide) is associated with higher rates of adherence to GLP-1 receptor agonist therapy compared with once-daily formulations (16–18), there is limited evidence regarding other potential factors that may support or deter GLP-1 receptor agonist therapy adherence and/or persistence (e.g., psychosocial factors, drug cost, and clinician support). Understanding these factors may assist in formulating strategies that encourage therapy persistence, resulting in improved glycemic control, more efficient health care utilization, and costs savings over time.

This article reports findings from a recent qualitative study that investigated key contributors to continuation and discontinuation of GLP-1 receptor agonist therapy in adults with type 2 diabetes. Our aim was to uncover information that may point to practical guidance for clinicians when initiating GLP-1 receptor agonist therapy and when providing ongoing needed support in the pursuit of greater adherence and persistence with therapy.

Research Design and Methods

Research Design

This noninterventional, cross-sectional, qualitative analysis used face-to-face interviews with adults with type 2 diabetes who had been treated with at least one GLP-1 receptor agonist formulation. The objective of the analysis was to enhance current understanding of participants' experiences, motivations, and challenges relevant to their persistence with GLP-1 receptor agonist therapy.

Setting and Participants

The interviews were conducted between 24 January and 1 June 2018 at six clinical sites in the United States (in the states of Alabama, Indiana, North Carolina, Ohio, Texas, and Washington). Inclusion criteria were ≥18 years of age, diagnosed with type 2 diabetes, and currently treated with a GLP-1 receptor agonist for at least 1 month at the time of screening or discontinued use of a GLP-1 receptor agonist within 1 year of screening but with a total of at least 1 month of treatment. The study protocol was approved by a central institutional review board (Quorum Review, Seattle, WA) and performed in accordance with Good Clinical Practice and applicable regulatory requirements. All eligible participants provided written informed consent and demographic data before being scheduled for their interview visit.

Assessment Tool

Interviews were conducted using a semi-structured qualitative interview guide that included open-ended questions and probes to obtain both spontaneous and prompted input from participants about their treatment experiences with GLP-1 receptor agonist therapy. The guide included discussion items designed to elicit information regarding participants' reasons for treatment continuation, adherence/nonadherence, or discontinuation. Key items covered initiation of GLP-1 receptor agonist therapy, interactions with their health care team, and psychosocial contributors (facilitators) to continuing or discontinuing therapy. Table 1 presents a sample of the questionnaire items. In response to these questions, "spontaneous offered" was selected on the interview grid when participants offered a response concept on their own. "Recognized probe" was selected if the interviewer asked a probing, follow-up question to elicit a concept response. "No effect" was selected when participants stated that they had not experienced the response concept.

Tool Development and Interviewer Training

The interview tool was developed by an experienced qualitative research group (Health Research Associates, Inc. [HRA], Mountlake Terrace, WA) in collaboration with the study sponsor. Four interviewers reviewed the content of the interview guides and participated in mock interview sessions with each other (led by senior research staff) to test the flow of the questions to find any problematic, slow, or awkward areas and to test the general timing of the interview.

A training day of observed practice interviews was organized with the HRA and study sponsor team and the study interviewers. Willing volunteers with type 2 diabetes were recruited from a local volunteer list to take part in the training interviews; no participant information or results of the practice interviews were recorded or retained. After the practice interviews, the interview guide was finalized, and

TABLE 1 Sample Questions From the Interview Guide

Key: Main questions are shown in boldface; follow-up probes are listed with bullets.

How do you feel it went with your (first/second) GLP-1 receptor agonist medication?
- Was using this medication easier, more difficult, or about as much work as you expected? (describe)
- What could have helped you to be more successful with it when you were first getting started? (more information from the doctor, better instructions printed on the device itself, fewer administration times, fewer side effects, etc.?)
- Was there anything about the product that made it particularly easy or particularly difficult to use?

The challenges you have described that make it harder for you to use GLP-1 receptor agonist medications are: _____. (read back to patients what they have listed as challenges)

Now I'm going to read a list of challenges some people report when using GLP-1 receptor agonist medications. As I read this list, please tell me if you remember experiencing any of these.

(Interviewer: ONLY ask follow-up probes on challenges if they have not already been mentioned.)
- Interruption of daily activities
- Health care team was not accessible to answer questions
- Health care team did not provide enough education/information
- Insurance issues (lack of coverage/out-of-pocket costs are high)
- Insufficient instructions on use of injectable or pen device
- Limited or inadequate instructions around GLP-1 receptor agonist starting dose and the need for increases in the dose
- Side effects (make sure patients detail these)
- Having to make changes in diet
- Fear of needles/self-injection
- Burden of many medications to take
- Discomfort from being first time with injectable medication
- Sense that medication was not working
- Did not see a need to keep taking the medication
- Frustration or discouragement related to having diabetes in general
- Weight gain or lack of weight loss (specify)
- No instruction around importance of exercise and minimizing food volume and dietary fat at meals
- Disappointed that it did not work as well as I expected

Of all of the challenges we have just discussed, which ones were the most difficult for you to deal with? (describe why) **Which ones are the most important?**

[For patients who discontinued] **Which of these challenges was a part of the reason you discontinued the GLP-1 receptor agonist medication?**

Which were the most important contributors to why you discontinued?

changes were submitted to the institutional review board for approval.

Data Collection

Four trained HRA research staff members conducted the interviews in a private room at the enrolled clinic sites. Each interview visit was audio-recorded and lasted ~90 minutes. On arrival at the scheduled interview session, participants were given a brief introduction to the interview purpose and process. They were reassured about the confidential nature of the interview contents and the personal information they provided. All interviews were conducted in English and directed by the semi-structured qualitative interview guide.

Analysis

Digital audio files of subject interviews were transcribed and entered into the ATLAS.ti software program v. 7.1.0 (19) for coding. The coding process was structured for thematic analysis, identifying patients' expressions of concepts, highlighting quotations to tag them in the coding program, and assigning a code stem to them so the data could be organized by similar content and used to build thematic pictures of patients' responses. As new concepts appeared in patients' responses in the transcripts, new categories were made to capture them in the coding framework. Some sections of the interview were used to compile actual full responses from patients against specific questions in instances in which showing the spectrum of replies against a research question was important. The interviews included a few rating exercises for symptom severity or symptom-related bother, for which patients were asked to give a rating on a numerical scale ranging from 0 to 10. Data from these exercises were used to develop descriptive quantitative tables.

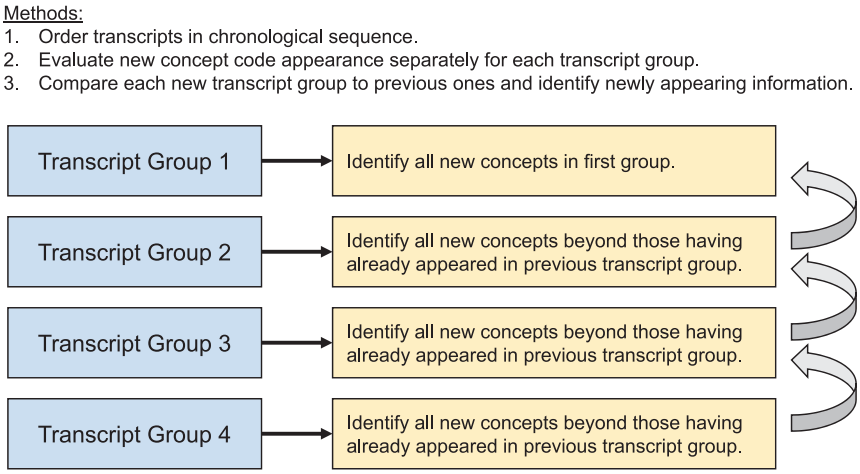

FIGURE 1 Method for evaluating saturation of concept.

Saturation of concept was assessed to determine whether a sufficient number of interviews had been conducted. Saturation of concept is reached when no new concepts are being identified in the interview data (20).

Transcripts were ordered chronologically based on interview completion date and then grouped into five groups of seven to eight transcripts each. Saturation was then evaluated by comparing the codes that were derived from the second transcript group with the codes that appeared in the transcripts from the first group to identify whether new information was still forthcoming. These evaluations and comparisons were repeated for each subsequent group. Once new information was no longer forthcoming, it was considered unlikely that further interviews with similar participants would have contributed any additional information or understandings (Figure 1).

Interrater agreement was used to assess consistency of code assignment. Two randomly selected interview transcripts were independently dual-coded and compared for percentage of agreement in the assignment of codes to concepts expressed by participants in the interview process.

Results

Thirty-six participants completed the qualitative interviews. Participants were predominantly older, female, and non-Hispanic White (Table 2). Participants who were currently on GLP-1 receptor agonist therapy at the time of the interviews (continuers) tended to have higher household incomes, shorter durations of diabetes, and lower A1C levels at the start of GLP-1 receptor agonist therapy than those who had stopped therapy (discontinuers). The 16 continuers were being treated with once-daily liraglutide, once-weekly exenatide, twice-daily exenatide, or once-weekly dulaglutide. Among the 20 discontinuers, which included discontinuation to one or more of all of the available GLP-1 receptor agonist formulations, 15 had discontinued GLP-1 receptor agonist therapy >6 months before their interview. The study did not include two recent additions to the GLP-1 receptor agonist class: once-weekly semaglutide and once-daily oral semaglutide.

Primary Facilitators Associated With GLP-1 Receptor Agonist Therapy Continuation

The number and percentages of continuers (n = 16) who identified primary facilitators for continuing GLP-1 receptor agonist use are presented in Table 3. The most commonly identified group of facilitators reflected participants' perception that the treatment was contributing to tangible, positive results (most importantly, glycemic control and weight loss). Some of the verbatim responses recorded during the interviews with GLP-1 receptor agonist therapy continuers are shown below.

> *"It helps my numbers so much, I don't want them to skyrocket again back above 8 [%]."*

> *"What made it easier was I knew the benefits . . . . I saw the weight loss . . . . So, that was a positive on my end."*

> *"The fact that it brought down my A1C would be the main thing."*

> *"A lower blood sugar, and like I said, it feels like it stabilizes my sugars and stops them from yo-yoing."*

> *"The knowledge of the cardiovascular benefit helped me stay on the GLP-1 [receptor agonist]."*

TABLE 2 Demographic Characteristics

	Continuers (n = 16)	Discontinuers (n = 20)
Age, years	58.3 ± 8.5	58.3 ± 8.9
Sex		
Male	5 (31.2)	5 (20.0)
Female	11 (68.8)	16 (80.0)
Highest level of education completed		
Some high school	1 (6.3)	2 (10.0)
High school graduate	5 (31.3)	6 (30.0)
Some college	7 (43.7)	11 (55.0)
Bachelor's degree	3 (18.7)	1 (5.0)
Current employment outside the home		
Employed part-time or full-time	11 (68.8)	5 (25.0)
Retired	2 (12.5)	4 (20.0)
Not employed	3 (18.8)	11 (55.0)
Annual household income, $		
5,000–14,999	2 (12.5)	1 (5.0)
15,000–34,999	–	7 (35)
35,000–49,999	3 (18.8)	5 (25.0)
≥50,000	9 (56.3)	7 (35.0)
Racial group		
White or Caucasian	13 (81.2)	18 (90.0)
Black or African American	2 (12.5)	–
Other	1 (6.3)	1 (5.0)
Unknown	–	1 (5.0)
A1C at start of GLP-1 receptor agonist, %	7.7 ± 0.9 (n = 12)	8.2 ± 1.4 (n = 10)
Most recent A1C, %	7.5 ± 1.3 (n = 16)	7.9 ± 1.9 (n = 19)
Diabetes duration, years	12.7 ± 7.5	15.3 ± 8.4
Duration of current GLP-1 receptor agonist therapy, months		
>6	13 (81.3)	–
<6	3 (18.8)	–
Time since discontinuation, months		
>6	–	5 (25.0)
<6	–	15 (75.0)
Current GLP-1 receptor agonist therapy		
Once-daily liraglutide	5 (31.3)	–
Once-weekly exenatide	4 (25.0)	–
Twice-daily exenatide	2 (12.5)	–
Once-weekly dulaglutide	5 (31.3)	–

Data are mean ± SD or n (%).

The other major category of facilitators represented an appreciation of reduced or absent treatment burden (e.g., "no side effects," "available or low cost," and "ease of use").

"For me, personally, I feel [GLP-1 receptor agonists in general] have less side effects or problems with medications than some of the other diabetic medications that are on the market."

"The insurance factor's one of [the biggest factor in using it], because they cover it."

I didn't have any side effects from the medication."

Primary Challenges Associated With GLP-1 Receptor Agonist Therapy Discontinuation

The most commonly identified challenges leading to treatment discontinuation reflected participants' disappointment with the same two categories—in this case, lack of treatment efficacy and/or enhanced treatment burden (e.g., medication side effects or high costs) (Table 3).

TABLE 3 Primary Facilitators and Challenges to Continued Use of GLP-1 Receptor Agonist Treatment

Continuers (n = 16 [100%])		Discontinuers (n = 20 [100%])	
Primary facilitators that contributed to continued GLP-1 receptor agonist use		Primary challenges that contributed to discontinued GLP-1 receptor agonist use	
[Blood glucose] numbers improved	8 (50.0)	Side effects	11 (55.0)
Weight loss	4 (25.0)	High cost	10 (50.0)
[Blood glucose] numbers controlled	3 (18.8)	[Blood glucose] numbers did not improve	5 (25.0)
No side effects	3 (18.8)	High frequency of administration	1 (5.0)
Available or low cost	3 (18.8)	[Blood glucose] numbers worsened	1 (5.0)
Easy to use	3 (18.8)	Discomfort or fear of needles or self-injection	1 (5.0)
Long-term benefits	3 (18.8)	Pain or bruising with injection	1 (5.0)

Data are n (%).

"I was having nausea."

"The insurance coverage was [the] main reason I discontinued . . . . Insurance stopped covering [it]."

"It didn't work . . . [My A1C] didn't go back up, it just never really went down anymore . . . went down a couple of points, and that was it."

Influence of the Health Care Setting on GLP-1 Receptor Agonist Continuation and Discontinuation

In general, both continuers and discontinuers broadly reported supportive experiences with their health care provider team when initiating a GLP-1 receptor agonist. However, it appeared that continuers were more likely than discontinuers to receive clinically relevant information from their health care team, including facts about GLP-1 receptor agonist medications, likely treatment benefits (e.g., how the new treatment would contribute to better glucose control), the importance of gradual dose titration, and the need to adjust diet after initiation), as well as ongoing support (i.e., the health care team making proactive calls to check on their progress).

Table 4 presents the percentage of participants who confirmed specific statements included in the questionnaire. In most areas, the majority of continuers, in contrast to discontinuers, confirmed that they had good communication with their health care team and that their questions about medication were answered and they were provided information about the importance of gradual dosage titration.

Discussion

Although recent studies have provided initial insights regarding various reasons for discontinuation of GLP-1 receptor agonist therapy, the contributors to therapy persistence have not been well defined or understood (15). To our knowledge, this is the first qualitative exploration of factors that may affect an individual's decision to discontinue or continue GLP-1 receptor agonist therapy.

In this qualitative study, we interviewed 36 individuals with type 2 diabetes who shared personal accounts of their experiences with GLP-1 receptor agonist therapy. Despite the uniqueness of their individual circumstances, we identified two broad participant-perceived factors associated with medication persistence or nonpersistence: perceived treatment efficacy and perceived treatment burden.

Regarding the first factor, we see that the majority of participants who continued therapy cited aspects of treatment efficacy, including "numbers improved" (50.0%), "weight loss" (25.0%), and "numbers controlled" (18.8%) as primary facilitators of persistence with their therapy. Conversely, efficacy concerns appeared to influence discontinuation, with 25.0% of discontinuers reporting that "numbers did not improve." At the heart of this behavioral concept, it is apparent that, when individuals sense that their treatment is contributing to positive, tangible benefits, they are more likely to feel motivated to continue to use it (21).

Regarding the second factor, continuers reported a reduction or absence of treatment burden, with as many as 18.8% of participants citing such factors as "no side effects," "available or low cost," and "easy to use" as crucial to why they continued on GLP-1 receptor agonist therapy. Not surprisingly, we see the converse among discontinuers, with "side effects" (55.0%) and "high cost" (50.0%) as the most common primary challenges to therapy persistence.

TABLE 4 Comparison of Facilitating Experiences: Continuers Versus Discontinuers

Experiences	Continuers (n = 16)	Discontinuers (n = 20)
Good communication with health care team		
• My health care team explained that GLP-1 receptor agonist therapy would improve my blood glucose control.	13 (81.3)	12 (60.0)
• My health care team explained why my GLP-1 receptor agonist medication needs to be taken as an injectable.	12 (75.0)	15 (75.0)
• My health care team explained the importance of gradual dosage titration.	12 (75.0)	10 (50.0)
• My health care team explained how to manage food volume and fats.	7 (43.8)	7 (35.0)
Access to information		
• My questions about medications were answered by my health care team when I started on GLP-1 receptor agonist therapy.	15 (93.8)	15 (75.0)
• I was provided information about GLP-1 receptor agonist medications.	15 (93.8)	12 (60.0)
• I was provided general information about diabetes.	12 (75.0)	14 (70.0)
• My physician's office called to check on my progress and ask if I had any additional questions.	10 (62.5)	8 (40.0)

Data are n (%).

The interplay between the perceived value of a medication and the perceived concerns (or sense of burden) about that medication is a well-studied phenomenon in the medication adherence literature (22), and both of these factors are seen as crucially important. Although they are typically considered to be modifiable factors, it is well recognized that the biological response to GLP-1 receptor agonist therapy can vary significantly depending on individuals' unique physiological characteristics, current level of glycemic control, and specific drug formulation (23). Therefore, lack of glycemic improvement, lack of weight loss, and/or intolerability of side effects may simply be an unmodifiable class effect in some participants, which could explain why 25.0% of discontinuers reported "numbers did not improve" as their primary reason for discontinuation. Although "high cost" was reported as a primary factor affecting therapy persistence, this issue can only be resolved through changes in payer reimbursement policies.

Nevertheless, our results suggest that several of these other key issues could potentially be addressed through more collaborative patient-clinician interactions before initiating therapy. For example, it appears that participants who continued with GLP-1 receptor agonist treatment were more likely than discontinuers to receive more comprehensive preparation and instruction at the start of treatment. As reported, 93.8% of continuers (vs. 75% of discontinuers) confirmed receiving information about GLP-1 receptor agonist medications and having their questions answered when starting therapy. Importantly, only 50% of discontinuers versus 75% of continuers confirmed receiving information about the importance of gradual dosage titration. This finding suggests that continuers may have been more likely than discontinuers to be started on a "low-dose" regimen at the time of initiation, which could account for the higher percentage of continuers versus discontinuers who reported "minimal or no side effects" with treatment: 87.5 versus 55.0%, respectively. Moreover, continuers were more likely than discontinuers (62.5 vs. 40%) to receive proactive phone contacts from their health care team during the first few months so that any concerns could be addressed. Through these interactions, participants likely received feedback on their progress, making them more aware of any tangible benefits (e.g., improved glycemic control, weight loss, cardiovascular benefits, and improved well-being) that might be accruing. It could also be that these patients were able to discuss with their health care team any issues they had with the therapy, which could have helped them overcome minor adverse effects.

This was an average sample size for qualitative research studies, and saturation of concept was achieved, indicating that a sufficient number of interviews had been conducted. However, given the large amount of individual variability found in this therapeutic area, the relatively small sample size limits the generalizability of these findings to the larger diabetes population. Additionally, participants' perceptions and continuation of therapy may have been affected by differences in GLP-1 receptor agonist formulations (e.g., frequency of administration and drug-specific side effects).

A key limitation is that no insurance coverage data were collected. Given that "high cost" was a common obstacle among discontinuers, it is reasonable to assume that more continuers versus discontinuers had insurance coverage for their medications. Additionally, because our population was heavily White/Caucasian, and there were no Black/African American participants in the discontinuer group, our findings cannot be generalized to the larger population of people with type 2 diabetes. Other limitations include self-selection for participation, dependence on participants' memories and/or articulation of their perceptions and experiences, and inability to exactly determine the range of previous GLP-1 receptor agonist medications that discontinuers may have tried.

Although larger, quantitative studies are clearly needed to confirm our findings and identify characteristics of each GLP-1 receptor agonist formulation that may affect treatment persistence, we believe the information and insights provided by the study participants may be useful to clinicians when initiating GLP-1 receptor agonist therapy, as these results point to strategies that could be adopted by health care providers to enhance perceived treatment efficacy while addressing and potentially resolving treatment burden issues. More specifically, these improvements could be accomplished by thoroughly informing patients about the potential benefits, limitations, and side effects of the medication. Doing this would prepare them with information and strategies to minimize any side effects that may arise. It would also provide ongoing support and feedback to highlight the tangible benefits of their therapy and help address any obstacles they may be encountering. Finally, these findings highlight the importance of insurance providers' coverage policies and ongoing access to GLP-1 receptor agonist medications, which will likely be a key driver of enhanced therapy persistence.

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W.P. has served as a consultant for Astra Zeneca, Dexcom, Eli Lilly, Intarcia, Mannkind, Merck, Novo Nordisk, Onduo LLC, and Sanofi. M.M. is an employee of Health Research Associates, Inc. C.G., N.I., and C.H. are employees of Novo Nordisk.

AUTHOR CONTRIBUTIONS

All authors designed the study, reviewed the data, and wrote the manuscript. M.M. provided statistical analysis. W.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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