Self-reported Barriers to Adherence and Persistence to Treatment With Injectable Medications for Type 2 Diabetes

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ABSTRACT

Purpose: This study explored the barriers that adult Americans experience when taking injectable medications for type 2 diabetes, from the time of filling the initial prescription through the decision to discontinue the medication.

Methods: An Internet-based survey was conducted in 2 waves among adult patients (N = 2000) who had received a physician prescription for insulin, liraglutide, or exenatide once weekly (QW), regardless of whether the prescription was filled by a pharmacy. In wave 1, patients were surveyed on their medication history and experience and, if relevant, the medication discontinuation process. Those still taking their injectable medication at the time of wave 1 were contacted 6 months later (wave 2, n = 585) to assess any changes in their medication experience.

Findings: Among patients who delayed filling their prescription by ≥1 week, cost was a common reason for delay for refilling of liraglutide (63%) and exenatide QW (49%). The most commonly reported barrier to maintaining injectable medication was injection concerns (42%) such as aversion to needles, pain, or needle size. Lack of perceived need was the most common reason for discontinuation for basal (47%) and prandial/premixed (44%) insulin. For liraglutide, the most common reason for discontinuation was experiencing an adverse event (33%); for exenatide QW, it was injection concerns (38%).

Implications: The diverse barriers we identified underscore the need for better patient–prescriber communication to ensure that newly prescribed injectable medications are consistent with a patient's ability or willingness to manage them, to appropriately set expectations about medications, and to address new barriers that arise during the course of treatment. (*Clin Ther*. 2016;38:1653–1664) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: adherence, discontinuation, injectable medication, persistence, type 2 diabetes.

INTRODUCTION

Patients with type 2 diabetes typically fail to address hyperglycemia with diet and exercise and require pharmacotherapy for disease control.[1,2] Adherence, defined by the World Health Organization as "the extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider," is necessary for disease control.[3] Nonadherence to antidiabetic medications results in poor long-term glycemic control and is consequently linked with diabetes-associated complications, more health care resource utilization, and higher costs.[4–9] Aikens and Piette[9] found a linear relationship between self-reported nonadherence and an increase in glycosylated hemoglobin levels measured 6 months later. Another study found that patients who were nonadherent to noninsulin antidiabetic medications, compared with adherent patients, were significantly more likely to be hospitalized or require an emergency department visit over a 1-year period.[7]

Medication nonadherence and nonpersistence, or discontinuation, have been shown to be particularly

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common among those taking injectable antidiabetic medications.[10] In a cross-sectional Internet survey of specialists and primary care physicians from 8 countries, including the United States, 73% of patients did not take insulin as prescribed.[11] Similarly, another analysis found those patients initiating treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs) had a 71% higher discontinuation rate in the first 6 months compared with those initiating saxagliptin, with discontinuation defined as a gap of ≥60 days without drug supply available as measured by using pharmacy claims.[12]

Nonadherence and nonpersistence to injectable antidiabetic medications are influenced by multiple factors such as tolerability, efficacy, cost of medications, complexity of a treatment regimen, and patient–provider interaction.[11,13–15] In particular, patients prescribed insulin have expressed facing additional difficulties in initiating and maintaining treatment that are not experienced by those taking only oral medications.[11,15] This issue is especially relevant because a national health interview survey conducted from 2010–2012 found that 29% of Americans with diabetes use insulin.[16] Past survey research analyzing injection burden with insulin has shown that patients think that injections are a serious burden, have a negative impact on quality of life, and would use injections more regularly if the pain could be relieved.[17]

However, to our knowledge, no previous studies have determined which of these difficulties are faced by patients initiating treatment with GLP-1RAs. The present study was designed to better understand the barriers to adherence and reasons for discontinuation that Americans with type 2 diabetes prescribed injectable medications face in multiple stages of their treatment, starting from the initial prescription through maintenance of the medication and finally to the decision-making process around discontinuation.

PATIENTS AND METHODS

Study Design

This study was a cross-sectional, Internet-based survey administered in 2 waves. Patients were recruited from all US census regions via the Harris Interactive Chronic Illness Panel or other third-party online research panels in the United States. These panels consist of participants who previously volunteered to complete health-based surveys, and they are not affiliated with any health care or insurance system. Survey invitations, including information for accessing the password-protected online survey, were e-mailed to panel members. Respondents eligible for the survey were US residents ≥18 years of age diagnosed with type 2 diabetes who reported ever being prescribed at least 1 of 4 injectable medication types: exenatide once-weekly (QW), liraglutide, basal insulin, or prandial/premixed insulin. These injectable medications were selected for study because they have a range of profiles in terms of dosing frequency, cost, adverse effects, and other attributes expected to be related to persistence. Exenatide QW is injected subcutaneously once weekly using a 23-gauge, 5/16″ needle.[18] Liraglutide is injected subcutaneously once daily, and pen needles are prescribed separately.[19] It is initiated at 0.6 mg per day for 1 week, and then titrated to a higher dose. Both exenatide QW and liraglutide can be administered any time of day, with or without meals.[18,19] The basal insulins that respondents reported receiving were insulin detemir and insulin glargine. These are administered once daily at the same time each day. The dose is individualized, and needles are prescribed separately. The prandial/premixed insulins reported by patients were insulin glulisine, insulin lispro, insulin human, regular human insulin, and insulin aspart.[20–27] These insulins can be injected with a pen device, using a vial and syringe, or via an insulin pump. Patient self-monitoring of blood glucose levels with dose adjustment is recommended.

Respondents who were prescribed a medication but did not have it filled by a pharmacy were considered eligible for relevant sections of the survey. Respondents were accepted until preset quotas for each medication and discontinuation status were filled ($N = 2000$). In cases in which patients stated that they had been prescribed >1 of the surveyed medications, patients were directed to answer questions about the medication type with the smallest number of respondents. We refer to the medication about which the patient answered questions as the "medication of interest."

In wave 1 of the study, patients were asked: (1) if they filled the medication of interest when first prescribed, time until filling the prescription, and, if filled, how long until they started taking it; (2) about their reactions to being prescribed an injectable; (3) for those initiating the medication of interest, if they discontinued using it; (4) for those discontinuing the

medication of interest, the reasons for discontinuing use and the decision-making process for discontinuation (ie, interactions with physicians and family); (5) if still taking the medication of interest, what barriers (if any) to taking it they experienced; and (6) demographic and clinical characteristics. Respondents also completed the Diabetes Empowerment Scale (DES), a measure of psychosocial self-efficacy for people with diabetes.[28] For questions eliciting reasons for a decision, respondents were allowed to select multiple reasons from a list and/or to provide a free-text reason. The order of reasons was randomly determined for each respondent. Respondents were then directed to select the main reason. Discontinuation was self-reported and included both patient-initiated discontinuation and physician-initiated discontinuation or switching. The investigators compiled the list of reasons for discontinuation by using previous studies of diabetic medications and from the clinical trials of the relevant pharmaceutical products. The online survey (including a preliminary list of reasons for discontinuation) was pretested with a small group of respondents (n = 12) and revised based on respondent feedback. Institutional review board approval of the study protocol and survey were obtained before distribution of the survey invitation.

Wave 2 of the survey was conducted 6 months later among respondents who were persistent with their medication of interest at wave 1 and agreed to be recontacted. These patients (585 respondents of the 1086 persistent patients who agreed to be recontacted) were asked whether they were still taking their medication of interest. If not, they were asked about the discontinuation process.

Data Analysis

For analysis, patients were classified into 8 subgroups: the 4 treatment groups (basal insulin, prandial/premixed insulin, liraglutide, and exenatide QW) further subdivided into those still taking their injectable medication ("continuers") and those who had discontinued use ("discontinuers"). Reported reasons for discontinuation and barriers to taking medication were categorized into 9 areas: lack of perceived need (eg, belief disease was already well managed); adverse events experienced (eg, hypoglycemia, weight gain, gastrointestinal events); injection concerns (eg, aversion to needles, needle size, pain); cost; health care provider recommendation (eg, stop or replace medication); burden/inconvenience (eg, blood glucose monitoring, injection frequency); lack of perceived medication benefits (eg, belief medication would not work); medication concerns (perceived but not experienced [eg, worry about potential weight gain]); and not understanding administration (eg, self-injection difficulty). (The **Supplemental Table** in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.009 lists reported reasons for discontinuation and barriers to taking medication.)

Demographic variables were reported as of wave 1. A weighting algorithm was applied so eligible respondents were appropriately representative of US residents ≥18 years of age with type 2 diabetes based on education, age, sex, race/ethnicity, region, and household income. Our weighting algorithm also adjusted for attitudinal and behavioral differences between those who are online versus those who are not, those who join online panels versus those who do not, and those who responded to this survey versus those who did not. Each respondent is given a score based on their reported information and then either weighted up (if they are underrepresented) or weighted down (if they are overrepresented). Using z critical values, 95% CIs for proportions were constructed.

RESULTS

At the time of contact for wave 1, a total of 2000 respondents completed the survey: 1155 continuers and 845 discontinuers, including 47 respondents who received medication but never filled their prescription (eg, only took samples) (**figure**). Wave 1 continuers interested in participating in the follow-up survey (n = 1086) were recontacted for wave 2. Of these, 585 were successfully recontacted and completed the wave 2 survey, with 522 (89%) indicating that they were still taking their medication of interest at that time and 63 (11%) discontinuing use since the time of wave 1 (classified as "discontinuers" for analytic purposes). Ten respondents were disqualified from further analysis because they provided conflicting information about their diagnosis and/or which medications they had been prescribed, yielding a total of 1092 continuers and 898 discontinuers across both waves.

Demographic and Baseline Characteristics

The mean age of respondents in each subgroup ranged from 54 to 58 years, except for exenatide QW

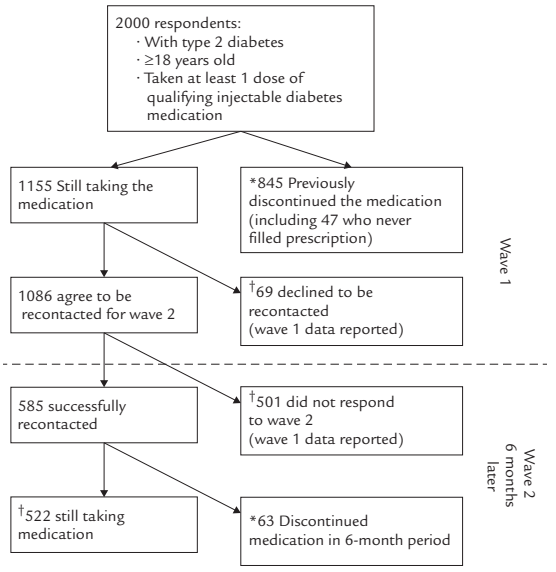

Figure. Flow diagram of study respondents. *Discontinued (reported under reasons for discontinuation in Table IV). †Continued (reported under medication barriers in Table IV).

discontinuers, who had a mean age of 46 years (Table I). Most respondents had health insurance (≥85%). The majority of patients reported hypertension or hypercholesterolemia. In the exenatide QW group, more patients (16%–21%) reported kidney disease than in the other groups. In addition, a high proportion of those who discontinued exenatide QW (37%) reported heart disease. Those who discontinued their medication were less likely to have health insurance compared with continuers, except for those prescribed prandial/premixed insulin. Discontinuers were also more likely to be injection-naive, with the exception of basal insulin users. The majority of patients who discontinued taking either exenatide QW or liraglutide did so during the first 6 months of treatment (79% and 50%, respectively).

Reaction to Being Prescribed Injectable Medication

Those patients who reported that the medication of interest was their first injectable diabetes medication (n = 1201) were asked about their reaction to being prescribed an injectable. Nervousness about using an injectable was common for those who initiated prandial/premixed insulin (46%–51%) or exenatide QW (48%–52%) treatment (Table II). Those patients initiating liraglutide therapy often had a positive reaction, with 44% of discontinuers and 55% of continuers reporting feeling encouraged that they could better manage their diabetes. Depending on the medication and discontinuation status, 4% to 10% of patients believed that their physicians were using injectable medications as a threat to encourage them to take control of managing their diabetes, except for those prescribed exenatide QW, for whom it was 24% to 28%.

Timing of Prescription Fill and Medication Initiation

When asked about the initial prescription, 2% of respondents reported never filling it. The proportion of respondents who delayed filling this prescription by at least 1 week was 11% to 18%, depending on the medication. Injection concerns were frequently cited as a reason for delay in filling prandial/premixed insulin and exenatide QW (30% and 56%, respectively, Table III), with nervousness about using an injectable commonly reported under this category (23% and 42%, respectively, data not shown). Cost was cited as a reason for delay by 63% and 49% of respondents prescribed liraglutide and exenatide QW. A high percentage of those prescribed liraglutide (31%) noted that they were given free samples and were therefore able to take the medication before filling the prescription.

Barriers Experienced by Those Still on Medication

When we asked patients still taking the medication of interest about their experience, the most commonly cited barrier to remaining on the medication was injection concerns (42%) (Table IV); specific concerns were preference for oral medications (23%), needle pain experience (13%), nervousness about using an injectable (11%), fear of needles (10%), and needle size (7%). Injection concerns were more commonly reported among those for whom the medication was the first injectable prescribed (49% [95% CI, 45–53]) compared with those with previous injectable experience (28% reporting injections concerns [95% CI, 24–32]). Burden/inconvenience was cited by 30% of continuers, with inconvenience of taking a medication that needs to be refrigerated most

Table I. Study population according to treatment discontinuation status.[*]

	Basal Insulin		Prandial/Premixed Insulin		Liraglutide		Exenatide QW	
Characteristic	Cont	D/C	Cont	D/C	Cont	D/C	Cont	D/C
No. (%) of patients	216 (36)	383 (64)	251 (42)	343 (58)	324 (54)	273 (46)	107 (54)	93 (46)
Mean age, y	54	58	58	56	56	57	46	54
% Male subjects	48	45	57	57	48	47	55	50
Race, %								
White	74	77	78	76	86	82	72	64
African American	18	18	18	17	11	10	17	25
American Indian or Alaska Native	5	1	0	2	0	1	2	5
Asian or Pacific Islander	1	1	1	1	1	2	3	4
Other	1	1	0	1	1	4	3	2[†]
Ethnicity, %								
Hispanic or Latino	10	14	18	13	14	13	14	7
Health insurance, %	85	93	89	86	91	98	94	99
Medicare	40	44	42	42	33	39	32	40
PPO	29	18	22	19	31	28	32	37
HMO	13	14	14	18	16	15	14	5
Other	7	4	9	7	3	5	2	5
Traditional	7	4	5	3	7	7	11	4
Medicaid	3	14	7	9	8	4	9	9
Comorbidity, %								
Hypertension	68	64	68	63	65	65	60	56
Hypercholesterolemia	64	66	66	60	63	66	70	73
Heart disease	17	19	14	12	12	18	37	10
Kidney disease	8	9	8	9	12	3	21	16
Mean DES score	3.86	3.81	3.83	3.85	3.78	3.81	3.97	3.91
First injectable, %	67	73	76	66	54	44	69	58
Delayed filling prescription by >1 wk, %	7	11	5	6	15	14	11	14
Never filled prescription, %	5	—	2	—	5	—	6	—
On medication for <6 mo before discontinuation, %	29	—	36	—	50	—	79	—

Cont = continued (ie, taking medication at time of survey); D/C = discontinued; DES = Diabetes Empowerment Scale; HMO = health maintenance organization; PPO = preferred provider organization; QW = once weekly.

[*]For wave 2 respondents, discontinuation status is based on wave 2 responses. For those only included in wave 1, the discontinuation status is based on wave 1 responses.

[†]Includes no response.

commonly mentioned (11%). Experiencing adverse events was a barrier for continuation in 24% of continuers. The primary adverse events noted by patients currently taking insulin were hypoglycemia (15%–16%) and weight gain (13%). Gastrointestinal adverse events were reported as a barrier by 6% to

Table II. Initial reaction to being prescribed an injectable medication for managing diabetes (≥20% for any group) among those for whom medication was first injectable taken. Values are given as percentage (95% CI).

	Basal Insulin		Prandial/Premixed Insulin		Liraglutide		Exenatide QW	
Reaction Choice Selected	D/C	Cont	D/C	Cont	D/C	Cont	D/C	Cont
I was nervous about using an injectable medication correctly	41 (33–49)	37 (31–43)	51 (44–58)	46 (39–53)	31 (24–38)	33 (25–41)	48 (35–61)	52 (37–67)
I felt encouraged that I could better manage my diabetes	34 (27–41)	39 (33–45)	28 (22–34)	43 (36–50)	44 (37–51)	55 (46–64)	41 (28–54)	36 (21–51)
I was disappointed that I had not managed my diabetes better to avoid using injectable medications	30 (23–37)	35 (29–41)	24 (18–30)	29 (23–35)	22 (16–28)	19 (12–26)	32 (20–44)	39 (24–54)
I was surprised because I thought my diabetes was being well managed	8 (4–12)	16 (11–21)	4 (1–7)	20 (14–26)	13 (8–18)	14 (8–20)	38 (26–50)	26 (13–39)
I felt that my doctor was using injectable medication as a threat to encourage me to take control of managing my diabetes	8 (4–12)	4 (2–6)	8 (4–12)	10 (6–14)	8 (4–12)	6 (2–10)	28 (17–39)	24 (11–37)

Cont = continued; D/C = discontinued; QW = once weekly.

Table III. Most commonly reported reasons for delay in filling prescription by ≥1 week. Values are given as percentage (95% CI).

Reason	Basal Insulin (n = 44)	Prandial/ Premixed Insulin (n = 34)	Liraglutide (n = 67)	Exenatide QW (n = 23)
Cost	21 (9–33)	17 (4–30)	63 (51–75)	49 (29–69)
Lack of perceived need	20 (8–32)	24 (10–38)	12 (4–20)	35 (16–54)
Injection concerns	19 (7–31)	30 (15–45)	22 (12–32)	56 (36–76)
Medication concerns (perceived)	10 (1–19)	13 (2–24)	5 (0–10)	23 (6–40)
Burden/inconvenience	5 (*–11)	19 (6–32)	11 (4–18)	32 (13–51)
Not understanding administration	3 (*–8)	2 (*–7)	4 (*–9)	15 (0–30)
Lack of perceived benefits	0 (0–0)	1 (*–4)	4 (*–9)	9 (*–21)
Other†	34 (20–48)	34 (18–50)	12 (4–20)	19 (3–35)

QW = once weekly.
*Negative lower bound to CI, indicating that the 95% CI includes 0.
†Includes reliance on samples, logistical barriers (eg, requirement to use mail order), and desire to use supplies of previously prescribed medications.

8% of patients currently taking GLP-1RAs but by ≤2% of those currently taking insulin.

Decision to Discontinue Medication

Overall, 898 respondents had discontinued the medication of interest: 845 had discontinued before the initial contact for wave 1, and an additional 53 had discontinued in the 6-month period before wave 2 contact. The decision for patients to discontinue their injectable medications was primarily made either jointly with (35%) or solely by (31%) their health care provider/physician, whereas 23% reported discontinuing on their own. Among all patients who discontinued, 78% reported being prescribed another medication as a replacement, but among the patients who discontinued their injectable medication on their own, only 65% reported ever receiving a replacement medication. For those patients who were prescribed insulin, 14% to 19% discontinued on their own compared with ~30% for either GLP-1RA.

Reasons for Medication Discontinuation

The most commonly reported reason for discontinuation overall and for insulin was lack of perceived need (Table IV). The most common reason for discontinuation of liraglutide was experiencing an adverse event; for exenatide QW, it was injection concerns. Similarly, when patients were asked about the main reason for discontinuation, lack of perceived need was the most cited main reason for basal and prandial/premixed insulin and overall (39%, 38%, and 29%, respectively). Experiencing an adverse event was the most common main reason for discontinuation for both liraglutide (32%) and exenatide QW (23%), and it was also the most commonly reported reason among those who discontinued prandial/premixed insulin during the first 3 months of treatment. When we solicited more details about adverse events, nausea or vomiting was cited as the main reason for discontinuation by 18% of patients who discontinued liraglutide and 3% of patients who discontinued exenatide QW; 8% of patients who discontinued insulin cited hypoglycemia as the main reason. Patients who discontinued liraglutide commonly cited cost and lack of perceived need as the main reason (23% and 16%), whereas those who discontinued exenatide QW cited injection concerns and burden/inconvenience as the main reason (22% and 14%).

Further calculations were conducted to evaluate the hypothesis that discontinuation in the first 6 months of treatment may represent the physician's decision to switch a patient from a GLP-1RA to insulin because of insufficient glycemic control. Among those who

Table IV. Barriers experienced and discontinuation reasons. Values are given as percentage (95% CI).

Variable	Medication Barrier Among Those Still Taking Medication					Discontinuation Reason Among Discontinuers									
						All Medications (n = 898)		Basal Insulin (n = 216)		Prandial/Premixed Insulin (n = 251)		Liraglutide (n = 324)		Exenatide QW (n = 107)	
	All Medications (n = 1092)	Basal Insulin (n = 383)	Prandial/Premixed Insulin (n = 343)	Liraglutide (n = 273)	Exenatide QW (n = 93)	C	M	C	M	C	M	C	M	C	M
Injection concerns	42 (39–45)	46 (41–51)	43 (38–48)	26 (21–31)	52 (42–62)	20 (17–23)	10 (8–12)	18 (13–23)	9 (5–13)	21 (16–26)	10 (6–14)	13 (9–17)	7 (4–10)	38 (29–47)	22 (14–30)
Burden/ inconvenience	30 (27–33)	34 (29–39)	34 (29–39)	18 (13–23)	24 (15–33)	11 (9–13)	4 (3–5)	7 (4–10)	1 (0–2)	11 (7–15)	4 (2–6)	6 (3–9)	2 (0–4)	37 (28–46)	14 (7–21)
Adverse events (experienced)	24 (21–27)	28 (24–32)	25 (20–30)	17 (13–21)	9 (3–15)	28 (25–31)	20 (17–23)	19 (14–24)	10 (6–14)	29 (23–35)	16 (11–21)	33 (28–38)	32 (27–37)	29 (20–38)	23 (15–31)
Medication concerns (perceived)	19 (17–21)	19 (15–23)	14 (10–18)	23 (18–28)	29 (20–38)	11 (9–13)	4 (3–5)	3 (1–5)	3 (1–5)	9 (5–13)	4 (2–6)	16 (12–20)	5 (3–7)	20 (12–28)	8 (3–13)
Lack of perceived need	9 (7–11)	9 (6–12)	10 (7–13)	7 (4–10)	13 (6–20)	36 (33–39)	29 (26–32)	47 (40–54)	39 (32–46)	44 (38–50)	38 (32–44)	19 (15–23)	16 (12–20)	31 (22–40)	12 (6–18)
Cost	2 (1–3)	1 (0–2)	1 (0–2)	7 (4–10)	4 (0–8)	13 (11–15)	12 (10–14)	11 (7–15)	10 (6–14)	5 (2–8)	5 (2–8)	25 (20–30)	23 (18–28)	6 (2–10)	6 (2–10)
Lack of perceived benefits	2 (1–3)	1 (0–2)	1 (0–2)	3 (1–5)	9 (3–15)	11 (9–13)	7 (5–9)	13 (9–17)	10 (6–14)	4 (2–6)	3 (1–5)	13 (9–17)	8 (5–11)	21 (13–29)	8 (3–13)
Not understanding administration	2 (1–3)	2 (1–3)	1 (0–2)	0 (0–0)	9 (3–15)	1 (0–2)	0 (0–0)	0 (0–0)	0 (0–0)	1 (0–2)	1 (0–2)	1 (0–2)	0 (0–0)	5 (1–9)	0 (0–0)
Health care provider recommendation	NA	NA	NA	NA	NA	14 (12–16)	12 (10–14)	17 (12–22)	16 (11–21)	19 (14–24)	18 (13–23)	7 (4–10)	4 (2–6)	8 (3–13)	7 (2–12)

C = cited as reason contributing to decision; M = main reason for decision; N/A = not applicable; QW = once weekly.

discontinued their medication in the first 6 months, the proportion who discontinued because of lack of perceived benefit was 9% for basal insulin (95% CI, 2–16), 1% for prandial insulin (95% CI, 0–3), 18% for liraglutide (95% CI, 12–24), and 23% for exenatide QW (95% CI, 14–32).

DISCUSSION

This study identified a diverse range of concerns that patients with type 2 diabetes faced when initiating or maintaining an injectable medication. Although some concerns were reported frequently across all medications, others were commonly seen for certain medication types.

Among these 4 types of medication, injection concerns were commonly faced, even among those still taking their injectable medication. Specifically, patients commonly reported nervousness about using an injectable, preference for oral medications, fear of needles, and needle size/pain as either a reason for delayed prescription fulfillment, a barrier to maintaining therapy, or a reason for discontinuation. These concerns are consistent with previous data showing that 33% of patients are anxious about taking their insulin injections.[29,30] For those who were prescribed exenatide QW, the relatively high frequency of injection concerns may be related to patient concern over the 8-mm, 23-gauge needle, the required mixing procedures, or the perception that physicians were using the prescription as a threat.[18,31]

Among patients prescribed insulin, the commonly reported lack of perceived need may be reflective of the large proportion of patients with diabetes who are asymptomatic and/or do not have their glycemic control monitored. These results are comparable with those found in a survey of patients with chronic diseases, including diabetes, in which lack of perceived need was mentioned as a common reason for medication nonfulfillment and nonpersistence in 25% and 23% of respondents, respectively.[32] The low proportion of continuers reporting lack of need (9%) may reflect that awareness of the need for glycemic control is a motivator to persist on treatment.[15] Burden/inconvenience was the second most cited barrier in this study for patients to maintain their insulin therapy, consistent with previous findings on the challenges of managing insulin.[29,30]

Not surprisingly, hypoglycemia and weight gain were specifically cited by patents on insulin therapy as both a barrier to maintaining treatment and a reason for discontinuation. These findings are consistent with previous research showing that experience and fear of hypoglycemia associated with insulin use can lead to decreased medication adherence, poorer adherence, and more perceived barriers to taking the medication.[33–35]

Weight gain is particularly problematic for patients with type 2 diabetes because many are already overweight at diagnosis.[36,37] In the DAWN (Diabetes Attitudes, Wishes and Needs) study, for example, 25.1% of patients with diabetes expressed substantial concern about their weight, which was associated with lower self-rated health, reduced adherence, poorer psychological well-being, and increased diabetes-related distress.[37]

For GLP-1RAs, after injection concerns, adverse events and perceived medication concerns were the most frequent barriers and reasons for discontinuation. Gastrointestinal adverse events, in particular, were cited as a barrier to continued use of GLP-1RAs. This finding is consistent with Phase III trial results in which nausea, vomiting, and diarrhea were common adverse events with the GLP-1RAs.[18,19] Burden/inconvenience was also frequently mentioned as a medication barrier and reason for discontinuation for patients using exenatide QW, potentially due to the mixing procedure that was required.[18,31]

The majority of patients discontinuing GLP-1RAs did so before 6 months of therapy. Some of the reasons for discontinuation cited by respondents previously taking GLP-1RAs are those likely to be experienced early in the course of therapy, such as injection concerns, adverse events, and cost. The economic burden of injectable drugs, particularly GLP-1RAs, may influence decisions on medication choice and persistence.[38,39] In a study of patients with type 2 diabetes from an economically burdened region in which up to 50% underused their medication, cost was cited as a primary reason for underuse.[38] Consistent with these findings, cost was cited in our study as a reason for delay in filling prescriptions, as a barrier to medication continuation, and as a reason for discontinuation. Those who discontinued a GLP-1RA in the first 6 months of therapy commonly reported lack of medication benefit as a reason. This pattern is consistent with the clinical scenario in which a patient is found to have insufficient glycemic control during the first 6 months of a new therapy and the physician therefore switches the patient to insulin.

Several of our findings suggest that patients either did not receive sufficient education on their injectable medication and/or did not retain key information from the training. For example, although patients taking insulin do not typically need to keep the product refrigerated, refrigeration was reported as a barrier to taking the medication. Unlike previous studies that found an association of low self-efficacy with resistance to using insulin and reduced adherence,[40,41] we found no difference in self-efficacy, based on DES score, between continuers and discontinuers. Research on psychological barriers to initiating insulin highlights concerns about self-efficacy to manage injections and the concept that some patients may feel that starting insulin reflects a personal failure to control their diabetes with other methods.[40] The similarly high DES scores for both continuers and discontinuers may be a consequence of the self-selected nature of the sample, but regardless, it shows that patients with high self-efficacy still find aspects of injectable antidiabetic medications to be barriers to maintaining therapy.

Because prescribers have reportedly used insulin as a threat to try to get patients to adhere to treatment recommendation,[15] we were interested in evaluating patient threat perception in the present study. Approximately 25% of patients prescribed exenatide QW perceived injectable medication being used as a threat to motivate behavior change, whereas this perception appeared to be less common for those prescribed insulin or liraglutide. In fact, the most common reaction among patients being prescribed liraglutide was feeling encouraged that they could better manage their diabetes. A report on barriers to insulin use by Polonsky and Jackson[42] suggests that one of the keys to helping patients overcome their individual barriers to initiation is for the prescriber to frame the medication positively.

It is notable that ~23% of patients discontinued medication without consulting their provider. Furthermore, 22% of patients who discontinued were not given a replacement medication, which may reflect a lack of knowledge on the part of the prescriber that the patient was no longer taking the injectable medication. If this decision was taken without discussion with their physician, the chance to prescribe a

replacement medication may have been missed. Understanding more about the decision-making process may encourage prescribers to better communicate with their patients to avoid gaps in treatment that could potentially lead to worsened glucose control and long-term complications.

Certain limitations apply to a study of this nature. Because patients who responded to the survey were not a random sample and were required to have a computer with Internet access, the representative nature of the study may have been affected. The high rates of insurance coverage mean that these results may not be generalizable to an uninsured population. A weighting algorithm accounting for demographic and attitudinal characteristics was applied to minimize the potential impact of selection biases.

An additional limitation of the survey was its retrospective nature and consequent dependence on the memory of respondents and potential for recall errors. Self-reporting of which medications were prescribed may not be accurate, although we took several steps to reduce errors, including providing visual images of the medication container. In addition, those using medication only for a short time may be less likely to remember and report having received it. In that case, these results may underrepresent the experiences of those who discontinued treatment quickly.

CONCLUSIONS

Our findings indicate the need to establish programs whereby information is routinely solicited from patients so that medication selection is consistent with patient preferences and ability/willingness to manage a particular medication. Once on medication, there is a need for ongoing monitoring and support to identify and address new barriers that arise. An example of such an initiative is the Medication Monitoring and Optimization Program utilized by community pharmacies in the Netherlands, which employed continuous patient-centered pharmaceutical care for those with chronic diseases to significantly reduce treatment discontinuation in patients with osteoporosis and hyperlipidemia.[43] Understanding a patient's thought process may aid physicians in motivating their patients to overcome barriers to filling and using prescribed injectable medication for type 2 diabetes.

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All authors were involved in the study and survey design, data interpretation, and manuscript editing. Dr Spain and Mr Wright were responsible for designing the tables and figures.

CONFLICTS OF INTEREST

Dr Spain, Dr Wivel, and Mr Martin were employees of GlaxoSmithKline at the time of the study and manuscript preparation; Mr Wright and Ms Hahn are employees of Harris Poll, which received funding from GlaxoSmithKline for this study. Dr Spain is now an employee of the ASPCA (American Society for the Prevention of Cruelty to Animals) and Dr Wivel is now an employee of Merck and Co., Inc. The authors have no other conflicts of interest related to this study or article.

SUPPLEMENTARY MATERIAL

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Table S1

Table S1. Reported reasons for discontinuation and barriers to taking medication by category for analysis.

Category for analysis	Reason
Injection concerns	• I was nervous about using an injectable diabetes medication
	• I prefer medications I can take by mouth (such as pills or tablets) instead of shots
	• I am afraid of needles
	• I was concerned about the needle size
	• I experienced needle pain from injecting
	• Testing my blood sugar was too inconvenient
Burden/inconvenience	• Testing my blood sugar was too painful
	• It was more of a hassle than it was worth
	• It was too difficult to plan my daily activities around the medication
	• It was too inconvenient to take a shot every day
	• It was too inconvenient to take a medication that needs to be refrigerated
	• It was too inconvenient to take a medication that had to be injected
	• I experienced skin lumps from the injections
Adverse events (experienced)	• I experienced itchiness, rash, or other reactions where the shot was injected
	• It made me gain weight
	• It made me feel more tired
	• It caused me to experience diarrhea, gas, or bloating
	• I experienced hypoglycemia (low blood sugar)
	• It made me sick to my stomach or made me throw up (nausea or vomiting)
	• I was worried that I would gain weight
Medication concerns (perceived)	• I was worried it would interfere with other medications that I take
	• I was worried that it would make me sick to my stomach or make me throw up (nausea or vomiting)
	• I read or heard news reports about problems with the medication
	• I was concerned that it was going to hurt my health
	• I did not think I needed to be on an injectable medication
Lack of perceived need	• I felt that my diabetes was being well managed without medication
	• I was able to manage my diabetes with changes to my diet and exercise
	• I lost weight another way (for example, diet or surgery)
	• The medication was too expensive
Cost	• My health insurance never paid for it
	• My health insurance stopped paying for it
	• The medication did not control my blood sugar well enough
Lack of perceived benefits	• I did not believe the medication would work
	• I was not sure how to use the medication
Not understanding administration	• I didn't understand the instructions for taking my medication
	• I wasn't sure how to give myself the injection
	• My doctor replaced it with a different medication
Health care provider recommendation	• My doctor took me off the medication without starting another one