

# Treatment-Related Attributes of Diabetes Therapies and How People with Type 2 Diabetes Report Their Impact on Indicators of Medication-Taking Behaviors

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**Purpose:** Understanding the treatment-related attributes influencing medication-taking behaviors in people with type 2 diabetes (T2D) is important for delivery of patient-centered care. This review aimed to identify and summarize studies in which people with T2D (PwD) directly indicated the treatment-related attributes associated with medication-taking behaviors or intentions.

**Materials and Methods:** EMBASE and PubMed were searched for studies (Jan 2005–May 2021) reporting the link between PwD-expressed diabetes treatment-related attributes and the decision to initiate, adhere to, or discontinue a T2D medication. Eligible studies reported attributes associated with oral antidiabetes drugs or injectables (not insulin). Studies not explicitly exploring the link between attributes and indicators of behaviors (eg most discrete-choice experiments [DCE] and those interrogating electronic medical records or claims databases) were excluded, as were studies where the link between attribute and behavior came from anyone but the PwD.

**Results:** Of the 6464 studies identified, 16 were included. Studies were conducted across multiple countries; the USA was most represented (n = 8 studies). The impact of treatment attributes was described on indicators of initiation (n = 3), adherence (n = 12), and discontinuation (n = 4). Some studies evaluated multiple behaviors. PwD perspectives were solicited by structured questionnaires (n = 10), qualitative approaches (n = 4), or DCE explicitly exploring the link to medication-taking behaviors (n = 2). Closed- (n = 9) and open-ended questions (n = 7) were employed. Across studies, several factors including glycemic efficacy (n = 9), weight change (n = 9), dosing frequency (n = 9), hypoglycemia (n = 8), gastrointestinal adverse events (n = 8), regimen complexity (n = 6), route of administration (n = 3), and cardiovascular risk (n = 1) were reported as influencing behaviors, being motivators or barriers to initiation, adherence, or discontinuation.

**Conclusion:** Several attributes influence how PwD take their medications. Insights gained directly from PwD have the potential to assist stakeholders in making more informed, patient-centered, treatment decisions, thus choosing and managing medications that PwD are comfortable initiating and persisting with over the longer term.

**Keywords:** adherence, discontinuation, type 2 diabetes, medication attributes

## Introduction

Medication adherence is the process by which people take their medications as prescribed with respect to the timing, dose, and frequency.<sup>1</sup> It has been described as comprising three different phases or behaviors including initiation, which occurs when an individual takes their first dose of prescribed medication; implementation, or the extent to which an individual's dosing corresponds to the prescribed regimen from initiation to the final dose; and discontinuation, which occurs when an individual decides, for whatever reason, to stop taking the prescribed medication.<sup>2</sup>

Optimization of treatment outcomes in people with type 2 diabetes (T2D) requires, firstly, that therapy is initiated in a timely manner, since therapeutic inertia can result in a prolonged period during which blood glucose levels are not at target leading to negative clinical, economic, and health-related quality of life (HRQoL) outcomes.<sup>3–5</sup> Once on an appropriate medication, it is important that patients follow the dosing recommendations of the healthcare team. Substantial evidence suggests that not using medication as advised is associated with suboptimal glycemic control, increased use of healthcare resources, and higher costs.<sup>6,7</sup> Finally, it is crucial that a person with diabetes (PwD) stays on

(persists with) an effective treatment and does not discontinue prematurely. However, it has frequently been reported and extensively reviewed that discontinuation rates are high among people with T2D, and this has a negative impact on clinical and economic outcomes.<sup>8,9</sup>

The treatment journey of PwD can be influenced by multiple different factors at initiation of therapy, during treatment itself, and at the point of discontinuation.<sup>6,10,11</sup> These factors may include patient, therapy, healthcare system, economic, support system, and psychosocial factors. Since delivery of patient-centered care that respects individual preferences and barriers is key in improving treatment outcomes,<sup>12,13</sup> it is of interest to understand which factors are particularly important to PwD; prescribing therapies that better meet their needs and expectations may facilitate medication adherence and persistence.

While there is considerable evidence regarding patient preferences and beliefs with respect to T2D therapies, the explicit linking of these with the different phases of medication-taking behaviors from the perspective of the PwD is less well studied. The aim of this review was, therefore, to identify studies reporting data that make the link between PwD-expressed treatment-related attributes and their impact on medication-taking behaviors to produce a resource that consolidates evidence on this topic.

## Materials and Methods

This review was conducted according to a protocol designed to limit the impact of reviewer bias, promote transparency and accountability, and improve the likelihood of accurate data extraction by describing the proposed approach, objectives, search strategy, study selection criteria, methods for data extraction and synthesis, and outcomes of interest that were specified a priori.

### Data Sources

Searches were undertaken in the EMBASE and PubMed bibliographic databases. In addition, abstracts presented at the most recent (2020 or 2021) congresses of the Professional Society for Health Economics and Outcomes Research (ISPOR, Global and European), the European Association for the Study of Diabetes (EASD), and the American Diabetes Association (ADA) were searched electronically on EMBASE or by hand if not indexed therein. A hand-search of the reference lists of eligible studies identified in the main review was also conducted.

### Search Strategy

Searches were run in May 2021 and included studies published since 1 January 2005. The main structure of the search consisted of seven concepts combined as follows: T2D AND medication-taking behaviors AND (non-specific drug therapy OR non-specific diabetes therapy OR specific named drug therapy groups) AND study types of interest AND PwD. The detailed syntax that was developed for each database to capture these general concepts is provided in the online [Supplementary Materials Tables S1](#) and [S2](#).

### Study Eligibility

Studies published in English were eligible for inclusion if they reported data regarding the link (or reported that there was no link) between PwD-expressed diabetes treatment attributes and medication-taking behaviors (eg initiation, taking, switching/changing, or discontinuation of a particular therapy) that came directly from adults ( $\geq 18$  years) with T2D and not from a healthcare professional (HCP) or another individual. Studies could have incorporated open-ended questions or included a list of reasons for certain medication-taking behaviors that were directly put to PwD.

Interventions were where there were any pharmacologic therapy for T2D; however, a decision was made following full-text review to exclude studies solely focused on treatment with insulin, although if insulin was one of several treatments included in a study, the findings were summarized. The variety of insulin formulations, regimens, and methods of delivery described in studies across a wide range of studies from both developed and less developed countries introduced a range of concepts, several of which had implications beyond the treatment itself. Furthermore, many of these studies did not reflect therapies currently used in clinical practice as the search included publications from 2005

onwards. Thus, the decision to exclude insulin was made to keep the review focused but does suggest a similar exploration of the published literature on people's attitudes to insulin use is warranted.

Eligible study types included those based on one-to-one or focus group interviews, surveys, other questionnaire-based studies, qualitative research, and patient diary studies. These types of study could be embedded in a broader investigation but were required to be a standalone component focused on the topic of interest of a relevant design. Discrete-choice experiments (DCE) or patient preference/satisfaction studies were only included if the link between treatment characteristics and medication-taking behaviors was explicitly explored.

## Study Selection

Two independent reviewers assessed the results obtained by the search strategy. Initial screening involved a broad review of the title and/or abstract of results to identify studies meeting or possibly meeting eligibility criteria. This was followed by full-text review of studies identified at screening. Records excluded at this stage were assigned an exclusion code and reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Discrepancies between reviewers were discussed until consensus was reached.

Data extraction was performed on a standardized data extraction form by two reviewers, with quality checking by a third. Variables extracted included study population, interventions, study type and methods of data collection, medication-taking behaviors impacted, and treatment attributes evaluated.

## Results

After de-duplication, the search identified 6464 records, of which 6347 were excluded at the first stage of review. Of 117 full-text publications, 101 were excluded (Figure 1) mainly because they did not report on medication-taking behaviors associated with treatment-related attributes. No additional studies were identified by searching relevant congress abstracts or citation searching of included publications. Thus, the final review included 16 studies.

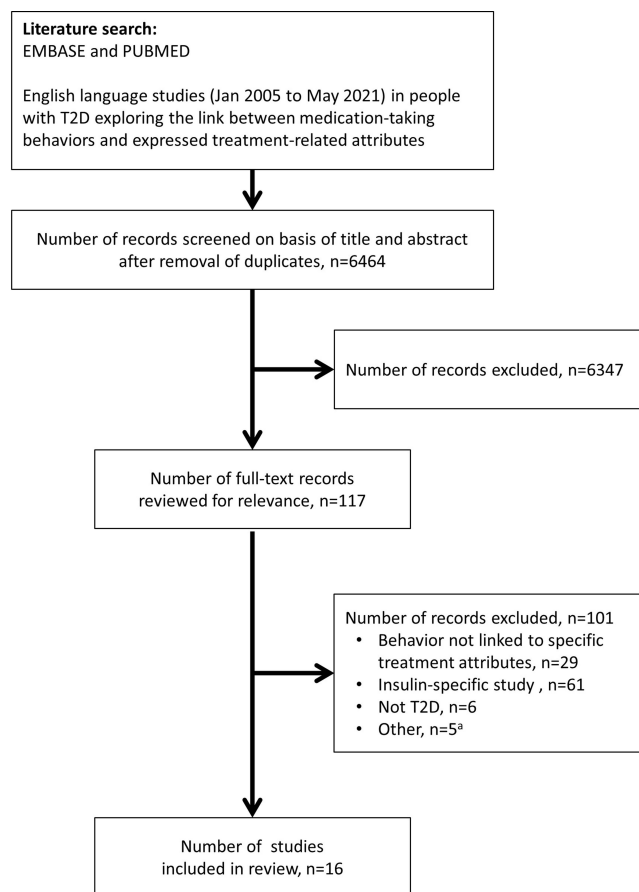
## Overview of Studies

An overview of the characteristics of the 16 included studies is provided in Table 1. Studies were conducted across a wide range of geographies, with the USA being the most represented country (n = 8 studies, including three multinational). Medication-taking behaviors evaluated included initiation of T2D medication (n = 2 studies), on-treatment adherence (n = 9), and discontinuation (n = 2). One study reported on both initiation and adherence behaviors, and two reported on reasons for both adherence and discontinuation. It became clear upon reviewing the evidence base that several of the studies evaluated the impact of treatment attributes, not on behaviors per se, but rather on indicators of initiation, adherence, and discontinuation. Thus, studies were also categorized according to whether PwD linked attributes to actual behavior (n = 10 studies) or to how they believe they would behave (n = 6 studies). These assessments have been based on our best understanding of how the studies were conducted.

Both oral and injectable T2D medications were evaluated across studies (Table 1). As per search inclusion criteria, all study populations comprised people with T2D, and sample sizes ranged from 22 to 2173 (Table 1). Mean age of participants was generally similar across studies (55.1–66.0 years) and in most, study populations comprised ~45–60% men.

Of the included studies, 10 employed structured questionnaires (including one with mixed qualitative and quantitative methods), four were qualitative studies, and two were DCEs. Study participants were queried regarding the attributes influencing their actual or hypothetical behaviors using both closed-ended questions (n = 9 studies), wherein they were provided with a list of possible alternatives from which they picked those relevant to their decision-making process, and open-ended questions where participants were free to voice any attributes that affected their decision-making (n = 7). Questionnaires that included closed-ended questions/lists were often generated from information gained by literature review and from clinical trials or product labels, then refined through pretesting in relevant patient populations.

In studies using a structured questionnaire, most reported the proportion of PwD indicating that a particular attribute impacted indicators of medication taking; two of these included Likert scales to determine the impact level of different attributes.<sup>14,15</sup>



**Figure 1** Study selection.

**Notes:** <sup>a</sup>Other reasons included reporting of psychologic rather than treatment-related factors in relation to medication-taking behaviors; study focused on preferences rather than adherence; literature review; not on prespecified medication-taking behaviors.

**Abbreviation:** T2D, type 2 diabetes.

Formal measures of adherence were employed in four studies: these included the Morisky Medication Adherence Scale (MMAS 4- or 8-item),<sup>14,16</sup> 5-item Medication Adherence Report Scale (MARS-5),<sup>17</sup> and the Adherence to Refills and Medications Scale for Diabetes score.<sup>18</sup> The remaining adherence studies did not employ formal measures: participants were simply asked questions regarding how their adherence may be affected by different factors. Most studies did not include any statistical analyses of the data.

## Attributes Impacting Indicators of Medication Taking

Several different treatment-related attributes were reported across studies that, in the opinion of the PwD, had an impact on indicators of medication taking (Table 1). These included glycemic efficacy (n = 9), weight change (n = 9), dose frequency (n = 9), hypoglycemia (n = 8), gastrointestinal (GI) adverse events (AEs) (n = 8), dose complexity (n = 6), route of administration (n = 3), and cardiovascular (CV) risk (n = 1). Some attributes were described under “umbrella” terms. Where this was the case, these attributes are summarized as part of the review, provided they were specifically noted by the study authors as being included in a broader category. With respect to AEs, these were only summarized if their nature (eg GI, hypoglycemia) was specifically described.

Overviews of the key findings according to attributes are provided in Tables 2–4.

## Glycemic Efficacy

Nine studies included evidence that the glycemic efficacy of T2D medications impacted medication-taking behaviors from the point of view of PwD. One study considered impact on initiation of treatment,<sup>15</sup> one on initiation and

**Table 1** Characteristics of Included Studies

Author (Year)/ Country	T2D Treatment	Study Type	Methods and Analysis	Medication-Taking Indicator	Hypothetical (H) or Actual (A) Behavior	Attributes Studied <sup>a</sup>	Study Population <sup>b</sup>
Barba et al, 2017 <sup>14</sup> Spain	Oral and/or injectable	Cross-sectional survey	Electronic self-administered questionnaire; PwD rate importance of a list of factors considered important for adherence (5-point Likert scale) Descriptive analysis; reported as % PwD reporting level of importance	Adherence (assessed by MMAS-4)	H	Complexity	N=963 Male, 49.9% Age, 60.4 (15.5) years T2D duration, 11.3 (8.9) years
Chen et al, 2020 <sup>25</sup> China	Insulin or GLP-1 RA	Cross-sectional survey	Interviewer-administered questionnaire; single- and multiple-choice questions providing a list of possible concerns that PwD had at treatment initiation Descriptive analysis; reported as % PwD responding a factor was of concern	Initiation	A	Weight change <sup>c</sup> Hypoglycemia <sup>c</sup> Dose frequency	N=500 Male, 48.2% Age, 55.1 (11.8) years T2D duration, 7.6 (6.4) years
de Climens et al, 2020 <sup>23</sup> UK, USA	OAD and/or injectables	Cross-sectional survey	Self-administered online questionnaire; comprised 1 closed- and 3 open-ended questions determining reasons for discontinuation Descriptive analysis; reported as % PwD stating factor was a reason for discontinuation	Discontinuation	A	Glycemic efficacy Weight change GI AEs Hypoglycemia	N=161 Age, ≥18 years
Dehdari and Dehdari, 2019 <sup>27</sup> Iran	T2D medications (not specified)	Qualitative study	Face-to-face interviews consisting of open-ended questions on experiences of adherence and its influencing factors Content analysis; presentation by themes and subthemes	Adherence	A	Dose frequency Route of administration	N=22 Male, 45.5% Age, 56.7 (9.2) years T2D duration, 9.3 (7.4) years
Farmer et al, 2006 <sup>17</sup> UK	OAD	Cross-sectional survey	Self-completed postal questionnaire; PwD rate agreement with list of beliefs about medication taking (5-point Likert scale) and state if factor affected their intention to take medication regularly Descriptive analysis; reported as % PwD agreeing with belief Spearman's rank correlation measures association between belief and adherence or intention	MARS-5 (Adherent=25; non-adherent <25)	H	Glycemic efficacy Weight change GI AEs <sup>c</sup>	N=121 Male, 52.1% Age, 66 (IQR 57–75) years T2D duration, 6 (IQR 1.7–8.2) years

(Continued)

**Table I** (Continued).

Author (Year)/ Country	T2D Treatment	Study Type	Methods and Analysis	Medication-Taking Indicator	Hypothetical (H) or Actual (A) Behavior	Attributes Studied <sup>a</sup>	Study Population <sup>b</sup>
Flory et al, 2019 <sup>20</sup> USA	Metformin	Qualitative study	Facilitator-led, semi-structured interviews and focus groups consisting of open-ended questions and probes on motivations and barriers to metformin Open coding following grounded theory approach; presented as 4 themes	Adherence	A	Glycemic efficacy Weight change GI AEs	N=20 Male, 55% Age, 32–81 years
Gater et al, 2020 <sup>22</sup> Canada, USA	Dual GLP-1/ GCG RA	Phase 2, double-blind, RCT (exploratory endpoint)	Self-administered electronic questionnaire (PQAT) consisting of 3 open-ended questions focused on benefits and disadvantages of treatments and reasons for willingness to/not to continue treatment Answers coded and grouped by concept using thematic analysis; reported as % PwD willing to continue medication	Adherence Discontinuation	H	Glycemic efficacy Weight change GI AEs	N=57 Male, 57.9% Age (range), 56.6 (33–77) years
Hauber et al, 2009 <sup>21</sup> UK, USA	OAD (hypothetical)	Cross-sectional DCE	Web-based survey; PwD rate (5-point Likert scale) likely adherence to hypothetical medication profiles (based on 6 attributes) presented in a series of choice tasks Ordered Probit analysis to establish effect of medication features on stated likelihood of adherence (controlled for PwD adherent to current medication)	Self-reported likelihood of missing or skipping doses	H	Glycemic efficacy Weight change GI AEs Hypoglycemia Heart attack risk	N=407 Male, 62% Age, 57 (12) years
Hauber et al, 2013 <sup>29</sup> USA	OAD (hypothetical)	Cross-sectional DCE	Web-based survey; PwD rate (5-point Likert scale) their likely adherence to the hypothetical medication profiles (based on 5 attributes) presented in a series of choice tasks Ordered Probit analysis to establish effect of medication features on stated likelihood of adherence	Self-reported likelihood of missing or skipping doses	H	Dose frequency Complexity	N=1114 Male, 53.8% Age, 62.1 (11.1) years

Huang et al, 2020 <sup>18</sup> USA	OAD and/or injectable	Qualitative study	Qualitative face-to-face semi-structured interviews consisting of open-ended questions on factors associated with adherence Content analysis; descriptive presentation by themes and subthemes	Adherence to Refills and Medications Scale for Diabetes Score (adherence: high =28; low <28)	A	Glycemic efficacy GI AEs Hypoglycemia <sup>c</sup> Complexity	N=23 Male, 48% Age range, 40–78 years
Jarab et al, 2018 <sup>28</sup> Jordan	OAD and/or injectable	Qualitative study	Facilitator-led focus groups comprising interviews using a schedule of open-ended questions including barriers to adherence Content analysis; descriptive presentation by themes	Adherence	A	Dose frequency Route of administration	N=36 Male, 72.2% Age, 30 to >70 years T2D duration, <5 to >15 years
Kubo et al, 2019 <sup>19</sup> Japan	OAD	Cross-sectional survey	Self-reported online questionnaire; PwD choose from list of motivations and influencers for initiation or adherence Descriptive analysis; reported as % PwD stating factor was a motivator/influencer	Initiation Adherence	A	Glycemic efficacy Dose frequency Complexity	N=560 Male, 85% Age, 56–63 years
Polonsky et al, 2011 <sup>15</sup> USA	QW injectable	Cross-sectional survey	Online questionnaire; PwD asked how a list of 6 treatment characteristics would influence willingness to take a new QW medication (5-point Likert scale) Reported as % PwD willing to take medication; responses compared according to current medication (chi-square tests)	Initiation	H	Glycemic efficacy Weight change Hypoglycemia Dose frequency Complexity	N=1355 Male, 54.8% Age, 58.0 (12.7) years T2D duration, 10.1 (7.8) years
Sajith et al, 2014 <sup>16</sup> India	T2D medications (unspecified)	Cross-sectional prospective, observational study	Interview using questionnaire (no details provided but appears PwD presented with list of factors affecting adherence) Descriptive analysis; reported as % PwD stating factor was a reason for nonadherence	Adherence MMAS-4 (adherence: 0=good; 4=very poor)	A	Hypoglycemia <sup>c</sup> Dose frequency Complexity	N=105 Male, 57.1% Age, 18 to >60 years T2D duration, <5 to >10 years

(Continued)

Table 1 (Continued).

Author (Year)/ Country	T2D Treatment	Study Type	Methods and Analysis	Medication-Taking Indicator	Hypothetical (H) or Actual (A) Behavior	Attributes Studied <sup>a</sup>	Study Population <sup>b</sup>
Sikirica et al, 2017 <sup>24</sup> France, Germany, Italy, Spain, UK, USA	GLP-I RA	Multinational, cross- sectional survey	Self-completed questionnaire consisting of series of open-ended questions about reasons for discontinuation Descriptive analysis; reported as % PwD stating factor was a reason for discontinuation (factors categorized from verbatim answers)	Discontinuation	A	Glycemic efficacy Weight change GI AEs Hypoglycemia Dose frequency Route of administration	N=2173 Male, 54.5% Age, 57.2 (10.4) years T2D duration, 316.4 (274.5) weeks
Spain et al, 2016 <sup>26</sup> USA	Insulin or GLP-I RA	Cross- sectional survey	Online questionnaire; PwD selected factors from a list that were barriers to adherence or reasons for discontinuation Descriptive analysis; reported as % PwD reporting factor was a barrier to adherence or reason for discontinuation	Adherence Discontinuation	A	Weight change <sup>c</sup> GI AEs Hypoglycemia <sup>c</sup> Dose frequency <sup>c</sup>	N=2000 Male, 45–57% Age, 46–58 years

**Notes:** <sup>a</sup>Only those attributes and reasons of relevance to the current review are listed. Attributes were referred to in various ways across studies, but terms have been standardized for reporting purposes; <sup>b</sup>Data are mean (SD) unless otherwise stated; <sup>c</sup>Denotes an attribute evaluated under a broader “umbrella” term. For the purposes of the review, the attribute must itself have been specifically noted by the study authors as being included under that umbrella either listed or provided as an example.

**Abbreviations:** AE, adverse event; DCE, discrete-choice experiment; GCG, glucagon; GI, gastrointestinal; GLP-I, glucagon-like peptide-I; IQR, interquartile range; MARS, Medication Adherence Report Scale; MMAS, Morisky Medication Adherence Scale; OAD, oral antidiabetes drug; PQAT, Patient's Qualitative Assessment of Treatment; PwD, people/person with diabetes; QW, once weekly; RA, receptor agonist; RCT, randomized controlled trial; T2D, type 2 diabetes.



**Table 2** Overview of Main Findings from Studies That Evaluated Glycemic Efficacy as a Treatment-Related Attribute

Indicator Influenced	Study (Author, Year)	Treatment Studied	Main Finding
Initiation	Polonsky et al, 2011 <sup>15</sup>	QW injectable	44% very/extremely likely to be willing to take medication if it “could help to reduce your blood sugar spikes”; current injectable users more likely to be willing vs current OAD users (65.1% vs 31.3%)
	Kubo et al, 2019 <sup>19</sup>	OAD	63.2% of drug-naïve PwD cited “reduces blood sugar effectively” as important when considering an OAD
Adherence	Farmer et al, 2006 <sup>17</sup>	OAD	91.5% agree/strongly agree with the belief that taking OADs regularly “would keep my blood sugar under control” and 87.8% that it “would keep my diabetes under control” (87.8%); both significantly correlated with intention to take medication (Spearman’s $r=0.49$ and $0.62$ , respectively; $p<0.001$ ), but not adherence ( $r=0.02$ and $0.10$ )
	Flory et al, 2019 <sup>20</sup>	Metformin	Under theme of “motivation”: benefits of glucose lowering (“My A1c has been fabulous”)
	Hauber et al, 2009 <sup>21</sup>	OAD	Glucose control had no effect on medication adherence
	Huang et al, 2020 <sup>18</sup>	Oral/injectable	Under theme “motivation for medication adherence” and subtheme “facilitators”: belief in the effectiveness of treatment, including perception that glucose control is a direct benefit of medication when taken according to HCP instructions (“If I didn’t take metformin, I’m sure my blood sugar level would go up very quickly. I think that’s dangerous ... ”)
	Kubo et al, 2019 <sup>19</sup>	OAD	43% of current users cited “reduces blood sugar effectively” as a motivation for continuing to take treatment
	Gater et al, 2021 <sup>22</sup>	GLP-1/GCG RA	32% reported improved glucose levels/control as reason reported for willingness to continue treatment
Discontinuation	de Climens et al, 2020 <sup>23</sup>	OAD/injectable	26% reported drug efficacy issues (of which 36% and 24% was no perceived positive benefit or decision of medical team, respectively) as a reason for discontinuation
	Sikirica et al, 2017 <sup>24</sup>	GLP-1 RA	34.5% reported inadequate blood glucose control as a reason for discontinuation

**Abbreviations:** GLP-1 RA, glucagon-like peptide-1 receptor agonist; GLP-1/GCG RA, dual glucagon-like peptide-1/glucagon receptor agonist; HCP, healthcare professional; OAD, oral antidiabetes drug; PwD, person/people with diabetes; QW, once weekly.

adherence,<sup>19</sup> five on adherence,<sup>17,18,20–22</sup> and two on discontinuation of therapy.<sup>23,24</sup> An overview of the key results regarding glycemic efficacy as an attribute influencing behavior indicators is provided in [Table 2](#).

Two studies indicated that when PwD are thinking about initiating a new treatment, efficacy is a key consideration.<sup>15,19</sup> For example, in a US online survey that provided a list of positive or negative characteristics of a once-weekly (QW) injectable, over 40% of study participants responded on a 5-point Likert scale that they would hypothetically be very or extremely likely to initiate such a treatment if it could help reduce blood sugar spikes.<sup>15</sup>

In qualitative studies in which PwD reported on their actual experiences with medications, blood glucose lowering was identified as a major motivation for medication adherence.<sup>18,20</sup> Similarly, in a cross-sectional survey, effective reduction of elevated blood sugar levels was chosen by PwD already on an oral antidiabetes drug (OADs) as a motivation to continue using prescription medication.<sup>19</sup> An exploratory analysis of a new patient-reported outcome measure embedded in a randomized controlled trial also reported that improved glucose levels/control was the most common reason for being willing to continue treatment with a dual glucagon-like peptide 1 (GLP-1R)/glucagon receptor (GCGR) agonist if it were offered.<sup>22</sup> However, in a UK general practice survey it was demonstrated that while a high proportion of

**Table 3** Overview of Main Findings from Studies That Evaluated Adverse Events of T2D Medications as a Treatment-Related Attribute

Indicator Influenced	Study (Author, Year)	Treatment Studied	Main Finding
<b>WEIGHT CHANGE</b>			
Initiation	Chen et al, 2020 <sup>25</sup>	Injectable	37.4% cited being “worried about AEs of injection therapy, such as hypoglycemia and <u>weight gain</u> ” as a concern regarding initiation of therapy
	Polonsky et al, 2011 <sup>15</sup>	QW injectable	55.1% very/extremely likely to be willing to take medication if it “could help you lose weight” (current oral vs injectable users: 44.0% vs 74.1%) and 51.5% if it “could help you to avoid weight gain” (39.3% vs 72.5%)
Adherence	Farmer et al, 2006 <sup>17</sup>	OAD	13.9% agree/strongly agree with the belief that taking OADs regularly “would lead to my gaining weight”, the only belief evaluated that was significantly correlated with reduced adherence (Spearman’s $r=-0.25$ ; $p<0.01$ ) although not significantly correlated with intention to take medication regularly ( $r=-0.12$ )
	Flory et al, 2019 <sup>20</sup>	Metformin	Under theme of “motivation”: “other benefits” including weight loss (“When I first started taking metformin, I lost about 50 pounds”)
	Gater et al, 2021 <sup>22</sup>	GLP-1/GCG RA	16% cited weight loss as a reason for willingness to continue treatment
	Hauber et al, 2009 <sup>21</sup>	OAD	Medication-related weight gain 1 of only 2 attributes (including heart attack risk) significantly associated with an increased likelihood of missing/skipping doses; a weight gain of 9.0 kg decreased the rate of likely adherence by 30% (95% CI 29.6, 32.3)
	Spain et al, 2016 <sup>26</sup>	Injectable	24% cited AEs (including weight gain) and 19% cited medication concerns (including weight worry) as barriers to adherence
Discontinuation	de Climens et al, 2020 <sup>23</sup>	OAD/injectable	18% who discontinued treatment due to side effects did so because of weight gain <sup>a</sup>
	Sikirica et al, 2017 <sup>24</sup>	GLP-1 RA	25% discontinued because treatment “did not help weight loss” and 8% because they “caused weight gain”
	Spain et al, 2016 <sup>26</sup>	Injectable	20%/28% cited AEs (including weight gain) and 4%/11% cited medication concerns (including weight worry) as main/contributory reason for discontinuation
<b>GI AEs</b>			
Adherence	Farmer et al, 2006 <sup>17</sup>	OAD	32.8% agree/strongly agree with the belief that taking OADs regularly “would cause me unpleasant side effects such as feeling sick or bloated”; belief not significantly correlated with intention to take medication (Spearman’s $r=-0.12$ ) or adherence ( $r=-0.08$ )
	Flory et al, 2019 <sup>20</sup>	Metformin	Under theme of “barriers to metformin use”: GI AEs (“The one side effect it gives me which is the runs”)
	Hauber et al, 2009 <sup>21</sup>	OAD	Mild stomach upset had no effect on medication adherence
	Huang et al, 2020 <sup>18</sup>	Oral/injectable	Under theme “motivation for medication adherence” and subtheme “barriers”: concerns about medication safety including side effects such as GI upset PwD reduced doses to avert side effects (“My stomach got so upset all the time. I got the diarrhea and I just felt better after I cut it off, and I left it at one ...”)
	Spain et al, 2016 <sup>26</sup>	GLP-1 RA	6–8% cited GI AEs as a barrier to current therapy

(Continued)

Table 3 (Continued).

Indicator Influenced	Study (Author, Year)	Treatment Studied	Main Finding
Discontinuation	de Climens et al, 2020 <sup>23</sup>	Oral/injectable	18% of PwD discontinuing treatment because of side effects did so because of GI disorders
	Gater et al, 2021 <sup>22</sup>	GLP-1/GCG RA	29% reported vomiting and 21% nausea as reasons for being unwilling to continue therapy
	Sikirica et al, 2017 <sup>24</sup>	GLP-1 RA	64% discontinued because treatment “made me feel sick” and 45% because they “made me throw up”
	Spain et al, 2016 <sup>26</sup>	Injectable	AEs most common reason for discontinuation of liraglutide (32%) and exenatide (23%), with nausea and vomiting the main reasons in liraglutide discontinuers (18%)
<b>HYPOGLYCEMIA</b>			
Initiation	Chen et al, 2020 <sup>25</sup>	Injectable	37.4% cited being “worried about AEs of injection therapy, such as hypoglycemia and weight gain” as a concern regarding initiation of therapy
	Polonsky et al, 2011 <sup>15</sup>	QW injectable	38.5% very/extremely likely to be willing to take medication if “you could have a lower risk of having hypoglycemia”
Adherence	Hauber et al, 2009 <sup>21</sup>	OAD	Mild-to-moderate hypoglycemia negatively impacted medication adherence if it occurred >2 times per month
	Huang et al, 2020 <sup>18</sup>	Oral/injectable	Under theme of “motivations for adherence” and subtheme “barriers”: concerns about medication side effects such as hypoglycemia impeded adherence
	Sajith et al, 2014 <sup>16</sup>	Unspecified	13.3% cited “other factors” including hypoglycemia as affecting medication adherence
	Spain et al, 2016 <sup>26</sup>	Injectable	24% cited AEs (including hypoglycemia) as a barrier experienced while on therapy
Discontinuation	de Climens et al, 2020 <sup>23</sup>	Oral/injectable	16% of those discontinuing medications because of side effects did so due to hypoglycemia <sup>b</sup>
	Sikirica et al, 2017 <sup>24</sup>	GLP-1 RA	10% discontinued due to “symptoms of low blood sugar”
	Spain et al, 2016 <sup>26</sup>	Injectable	20%/28% cited AEs (including hypoglycemia) as the main/contributory reason for discontinuation

Notes: <sup>a</sup>6.2% in whole study population; <sup>b</sup>5.6% in whole study population.

Abbreviations: AE, adverse event; CI, confidence interval; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GLP-1/GCG RA, dual glucagon-like peptide-1/glucagon receptor agonist; OAD, oral antidiabetes drug; PwD, person/people with diabetes; QW, once weekly; T2D, type 2 diabetes.

study participants agreed or strongly agreed with the beliefs that taking OADs regularly would keep their “blood sugar under control” or that regular OADs would keep their “diabetes under control”, these beliefs were not found to be significantly correlated with self-reported adherence as measured using MARS-5.<sup>17</sup> In addition, a DCE that directly linked preferences for treatment attributes to the likelihood of people with T2D missing or skipping doses of a hypothetical OAD also found that the attribute of glucose control had no impact on this indicator of adherence.<sup>21</sup>

PwD who had discontinued medication in the previous 6 months commonly cited drug efficacy issues including no perceived positive benefit and inadequate blood glucose control as reasons for which they stopped treatment of OADs and injectable medications (Table 2).<sup>23,24</sup>

**Table 4** Overview of Main Findings from Studies That Evaluated Dosing Characteristics (Frequency, Complexity, and Route) of T2D Medications as a Treatment-Related Attribute

Indicator Influenced	Study (Author, Year)	Treatment Studied	Main Finding
<b>DOSE FREQUENCY</b>			
Initiation	Chen et al, 2020 <sup>25</sup>	Injectable	58% reported inconvenience of daily injections as a concern regarding initiation
	Polonsky et al, 2011 <sup>15</sup>	QW injectable	36.5% agreed/strongly agreed that “QW medication could help me stick to my blood glucose-lowering medications better”
	Kubo et al, 2019 <sup>19</sup>	OAD	Important factors when considering an OAD in drug-naïve PwD: “has a weekly dosing schedule” (5.2%); “don’t have to take it every day” (10.4%); “has a daily dosing schedule” (12.1%); “less frequent dosing schedule” (32.9%) 17.4% cited “drug has a better dosing schedule in that it is less frequent” as motivation for initiation
Adherence	Dehdari and Dehdari, 2019 <sup>27</sup>	Unspecified	Under theme “perceived barriers to adherence” and subtheme “treatment characteristics”: PwD indicated that taking medications several times a day may affect adherence
	Hauber et al, 2013 <sup>29</sup>	OAD	Higher likelihood of non-adherence with less convenient dosing (fewer pills and lower frequency)
	Jarab et al, 2018 <sup>28</sup>	Oral/injectable	Under theme “barriers to adherence”: many PwD related non-adherence to frequency of administration (“If it could be made that you can take all your medicines in one go that would be better than having different periods”)
	Kubo et al, 2019 <sup>19</sup>	OAD	Important factors when considering an OAD in current users: “has a weekly dosing schedule” (4.3%); “don’t have to take it every day” (4.0%); “has a daily dosing schedule” (37.3%); “less frequent dosing schedule” (28.4%) 14.5% cited “drug has a better dosing schedule in that it is less frequent” as motivation for continued treatment
	Sajith et al, 2014 <sup>16</sup>	Unspecified	18.1% reported “frequency of dosing/increasing number of dosing times” as a factor affecting adherence
	Spain et al, 2016 <sup>26</sup>	Injectable	30% cited “burden/inconvenience” (including dose frequency) as a barrier experienced on therapy
Discontinuation	Sikirica et al, 2017 <sup>24</sup>	GLP-I RA	20.1% discontinued because “regular injections were too inconvenient”
	Spain et al, 2016 <sup>26</sup>	Injectable	4%/11% cited “burden/inconvenience” (including dose frequency) as a main/contributory reason for discontinuation
<b>COMPLEXITY</b>			
Initiation	Polonsky et al, 2011 <sup>15</sup>	QW injectable	61.3% agreed/strongly agreed that “QW medication could make taking that specific blood glucose-lowering medication more convenient”; 38.3% very/extremely likely to be willing to initiate medication “if it reduced number of daily OADs”
	Kubo et al, 2019 <sup>19</sup>	OAD	31.2% of drug-naïve PwD cited treatment being “easy to take or administer” an important factor when considering an OAD; 4.3% cited “drug is more convenient to take” and 8.7% “I wouldn’t have to take as many medications” as motivations for initiation

(Continued)

**Table 4** (Continued).

Indicator Influenced	Study (Author, Year)	Treatment Studied	Main Finding
Adherence	Barba et al, 2017 <sup>14</sup>	Oral/injectable	81.6% reported “complexity of administration” and 57.2% “complexity of medication container” as important factors associated with adherence
	Hauber et al, 2013 <sup>29</sup>	OAD	Higher likelihood of non-adherence with less convenient dosing (fewer pills and lower frequency)
	Huang et al, 2020 <sup>18</sup>	Oral/injectable	Under theme of “other barriers” and subtheme of “barriers”: complexity of regimen (comprising type, frequency, quantity, and size) suggested as an impediment to adherence
	Kubo et al, 2019 <sup>19</sup>	OAD	39.6% of current users cited treatment being “easy to take or administer” an important factor when considering an OAD; 21.5% cited “drug is more convenient to take” and 6.3% “I wouldn’t have to take as many medications” as motivations for continuing treatment
	Sajith et al, 2014 <sup>16</sup>	Unspecified	19.1% cited “complexity of medication regimen” and 25.7% “number of medications/too much medication” as factors affecting medication adherence
<b>ROUTE OF ADMINISTRATION</b>			
Adherence	Dehdari and Dehdari, 2019 <sup>27</sup>	Unspecified	Under theme of “medication beliefs” and subtheme “prioritizing use of pills instead of insulin injection”: preference for pills was identified as a variable influencing adherence (“Pills are [less] bothering than seeing the injection”)
	Jarab et al, 2018 <sup>28</sup>	Oral/injectable	Under theme “barriers to adherence”, many PwD related non-adherence to route of administration, preferring any other route than injectable (“I would prefer it if it wasn’t for the needle. If there was another way of taking it”)
Discontinuation	Sikirica et al, 2017 <sup>24</sup>	GLP-I RA	39.7% stated that preferring oral medication over injections was a reason for discontinuation

**Abbreviations:** GLP-I RA, glucagon-like peptide-I receptor agonist; OAD, oral antidiabetes drug; PwD, person/people with diabetes; QW, once weekly; T2D, type 2 diabetes.

## Weight Change

Weight change was evaluated in nine studies as an attribute influencing medication-taking indicators. Two studies evaluated its potential impact on indicators of initiation,<sup>15,25</sup> four on indicators of adherence,<sup>17,20–22</sup> two on discontinuation,<sup>23,24</sup> and one on both adherence and discontinuation.<sup>26</sup> An overview of key findings from studies reporting on weight change is provided in [Table 3](#).

Studies indicate that AEs associated with T2D medications such as weight gain could be an important consideration for PwD at initiation of therapy. For example, over half of PwD included in a US cross-sectional survey reported that hypothetically they would be very or extremely willing to take a QW injectable if it could help avoid weight gain or promote weight loss.<sup>15</sup>

In several studies, PwD also indicated that weight gain was a barrier<sup>17,21,22,26</sup> or that weight loss was a motivator<sup>20,22</sup> to treatment adherence. Indeed, in a UK cross-sectional survey, the belief that taking OADs regularly would lead to weight gain was the only belief evaluated that was correlated with lower adherence (MARS-5) (Spearman’s  $r = -0.25$ ;  $p < 0.01$ ) although it was not correlated with intention to take medication ( $r = -0.12$ ).<sup>17</sup> Similarly, in a DCE, Hauber et al<sup>21</sup> demonstrated that medication-related weight gain was one of the only treatment attributes of a hypothetical OAD that was significantly associated with a higher likelihood of PwD missing or skipping doses (p-value not provided) ([Table 3](#)).

Discontinuation of T2D medications may also be influenced by weight changes, as reported in three cross-sectional surveys.<sup>23,24,26</sup> For example, in a study that used data from the Adelphi Diabetes Disease Specific Programme (DSP), two of the reasons for which previous GLP-1 RA users said they had stopped therapy in the prior 6 months were that treatment had not helped them to lose weight or had caused weight gain.<sup>24</sup>

## GI Adverse Events

Nine studies included an evaluation of GI AEs as a treatment-related attribute impacting medication-taking indicators. Attributes were predefined in five of these studies, while in the remaining four, participants indicated attributes of importance themselves. Table 3 provides an overview of study results with respect to GI AEs.

No studies were identified that linked GI AEs with the decision to initiate T2D medication, but several evaluated the impact of GI AEs on adherence indicators ( $n = 5$ ). For example, in two qualitative studies, PwD stated that in their experience GI AEs had been barriers to use of both oral and injectable medications, with some individuals indicating that they had reduced doses to avoid these AEs.<sup>18,20</sup> Another two studies, however, failed to demonstrate that GI AEs impacted adherence indicators. Farmer et al reported that, while nearly one-third of PwD agreed or strongly agreed with the belief that taking OADs regularly would “cause unpleasant side effects such as feeling sick or bloated”, the belief was not significantly correlated with either medication adherence or intention to take medication (Spearman’s  $r = -0.08$  and  $-0.03$ , respectively).<sup>17</sup> It was also demonstrated in a DCE that the attribute of mild stomach upset had no effect on the likelihood of PwD missing or skipping doses of a hypothetical OAD.<sup>21</sup>

Three studies demonstrated that GI AEs had been the reason for discontinuation of medication in 18–64% of people, depending on the study (Table 3).<sup>23,24,26</sup> Gater et al reported that nausea and vomiting were the most common reasons for which PwD who had received a dual GCG/GLP-1 RA in an RCT would be unwilling to continue treatment with the same medication.<sup>22</sup>

## Hypoglycemia

Eight studies provided evidence that hypoglycemia may influence the way people with T2D take their medications. The impact of hypoglycemia on indicators of initiation was evaluated in two studies,<sup>15,25</sup> on adherence indicators in four,<sup>16,18,21,26</sup> and on discontinuation in three.<sup>23,24,26</sup> Table 3 provides a summary of the main findings from these studies.

Hypoglycemia was frequently included under a broader category rather than reported as a single attribute. For example, one study that retrospectively evaluated the concerns that PwD currently taking injectable therapy had upon initiation of that treatment found that over one-third of participants were “worried about AEs of injection therapy”, and this included both hypoglycemia and weight gain.<sup>25</sup> However, in another study, PwD indicated that having a lower risk of hypoglycemia specifically would hypothetically make them very or extremely willing to take a QW injectable medication (Table 3).<sup>15</sup>

With respect to indicators of adherence, three studies included hypoglycemia as an example under a broader category of attributes that were viewed by PwD as a barrier to adherence.<sup>16,18,26</sup> However, in their DCE, Hauber et al<sup>21</sup> found that hypoglycemia only negatively impacted adherence with a hypothetical OAD if it occurred more than twice per month.<sup>21</sup> In the two discontinuation studies that specifically included hypoglycemia as an attribute, only a relatively small proportion of PwD indicated that it had been a reason for their stopping therapy.<sup>23,24</sup>

## CV Risk

A single study evaluated the impact of CV risk on medication taking.<sup>21</sup> Along with weight gain, CV risk was the only other attribute studied in the DCE by Hauber et al<sup>21</sup> that had a significantly negative impact on the likelihood of PwD missing or skipping doses of a hypothetical OAD. A 1% increase in the risk of heart attack resulted in a 16.5% (95% CI 16.1, 17.0) reduction in likely OAD adherence.

## Dose Frequency

Dose frequency was reported as a treatment attribute impacting medication-taking indicators in nine studies. The influence of dose frequency on indicators of initiation was evaluated in two studies, on adherence indicators in six studies, and on discontinuation in two studies. Key results from each of these studies are detailed in Table 4.

When considering initiation of medication, treatment-naïve PwD indicated that they had concerns regarding the inconvenience of frequent dosing schedules and that less frequent schedules were a motivating factor.<sup>19,25</sup> Similarly, dose frequency was also cited as a barrier to medication adherence in both qualitative studies<sup>27,28</sup> and cross-sectional surveys.<sup>16,19,26</sup> In addition, a DCE that linked treatment attributes of a hypothetical OAD to an indicator of medication adherence demonstrated that people with T2D were increasingly likely to miss or skip OAD doses as dose frequency and pill burden increased.<sup>29</sup> Two cross-sectional surveys also provided evidence that the inconvenience of frequent injections had led to some PwD discontinuing medication.<sup>24,26</sup>

## Regimen Complexity

Regimen complexity was described in a variety of ways across the six studies in which it was evaluated as a feature influencing medication taking. Features such as convenience, ability to reduce doses of other glucose-lowering agents, and complexity of administration or medication container were all assumed to reflect regimen complexity in some way. Two studies reported on the influence of complexity on indicators of treatment initiation<sup>15,19</sup> and five on adherence indicators.<sup>14,16,18,19,29</sup> The main findings from these studies are presented in Table 4.

Convenience, ease of use, and reduction in other medications were all cited as important motivations for initiating treatment.<sup>15,19</sup> For example, Polonsky et al reported that a substantial proportion of PwD agreed or strongly agreed that they would be hypothetically willing to take a QW injectable with such features (Table 4).<sup>15</sup> Studies evaluating the impact of treatment attributes on indicators of adherence reported similar findings.<sup>14,16,18,29</sup> For example, in a qualitative study, PwD stated that complexity of regimen comprising type, frequency, quantity, and size of medication had negatively impacted their adherence to medication.<sup>18</sup> Furthermore, in a prospective observational study, participants cited complexity of medication regimen as a cause of self-reported non-adherence.<sup>16</sup> Two more studies revealed that adherence was hypothetically impeded by regimens of greater complexity.<sup>14,29</sup>

## Route of Administration

Findings from three studies indicated that route of administration could have an impact on how PwD take their T2D medications (Table 4).

No studies were identified that explored the impact of route of administration on the decision to initiate medication. However, in two qualitative studies PwD reported that in their experience, injection was a barrier to adherence.<sup>27,28</sup> In addition, nearly 40% of PwD who discontinued GLP-1 RAs indicated that they did so because of a preference for the oral over injectable route of administration.<sup>24</sup>

## Discussion

This review identified a range of different treatment-related attributes that people with T2D directly or indirectly implicated in medication taking across all parts of the treatment journey. These findings are both consistent with and add to the broader evidence base on the aspects of treatment that people with T2D value.

Treatment efficacy emerged as an important consideration for PwD in deciding whether to initiate a medication and as a motivating factor to take their medication; studies also suggested that inadequate glycemic efficacy may cause PwD to discontinue therapy. Similar findings have been more recently reported in a study that, while meeting eligibility criteria for this review, was published outside of the date cut-off. In a non-interventional, cross-sectional qualitative study in people with T2D who had received treatment with  $\geq 1$  GLP-1 RA, improvements in, or control of, blood glucose were cited as facilitators to adherence in 50.0% and 18.8% of study participants who continued treatment with a GLP-1 RA, respectively.<sup>30</sup> Furthermore, among participants who discontinued treatment, 25% did so due to no improvement and 5% because of worsening of blood glucose. Taken together, the findings on direct elicitation of PwD opinions on reasons for medication-taking behaviors align with other published studies that employed formal patient preference assessments to demonstrate that glycemic management is an important driver of patient preference.<sup>31,32</sup>

Weight was also shown to be a factor that may influence the decision to initiate, continue treatment with, or discontinue a T2D medication. These observations are largely consistent with other evidence demonstrating an association between weight loss and better medication adherence<sup>33–35</sup> or lower rates of discontinuation in people with T2D.<sup>36,37</sup>

It should, however, be noted that although the relationship between weight and discontinuation appears to be relatively straightforward, this might not always be the case with weight and adherence, as suggested in a recent narrative review.<sup>38</sup> Formal patient preference assessments have also demonstrated that people with T2D value therapies with weight-loss properties.<sup>39–41</sup> In fact, in a Spanish DCE (willingness-to-pay approach), it was reported that avoiding weight gain of 3 kg per 6 months was the most highly valued treatment attribute of oral or injectable therapies.<sup>42</sup> Similarly, in another study, avoiding a 5-kg weight gain was 1.5–2.3-fold more important than achieving moderate glycemic control among people with T2D from Germany and Sweden.<sup>43</sup>

The weight profile of any given medication is likely to be an important attribute to people with T2D: excess weight has been linked to several negative sequelae, including worse glycemic management<sup>44</sup> and increased risk of microvascular and macrovascular complications.<sup>45,46</sup> Indeed, a recent expert opinion review by Lingvay et al reinforces the clinical importance of weight reduction for people with T2D and confirms that weight loss should be a primary approach in many individuals.<sup>47</sup> Furthermore, individuals with T2D and higher body weight may have worse HRQoL.<sup>48–50</sup> In addition, weight gain has been reported to be significantly associated with lower rates of overall treatment satisfaction.<sup>48</sup> This observation is consistent with findings from the study by Polonsky et al included in the current review, where it was demonstrated that people with T2D and low treatment satisfaction on their current OAD medication were more willing to initiate treatment with a hypothetical QW injectable therapy if it contributed to weight loss, compared with study participants who were highly satisfied with their current medication.<sup>15</sup>

GI AEs are commonly experienced by PwD treated with T2D medications,<sup>51</sup> and we identified several studies suggesting that these symptoms influence medication adherence and discontinuation indicators. These findings are again consistent with those from formal preference assessments wherein people with T2D place greater value on treatments with lower rates of GI AEs.<sup>31,32</sup> Indeed, the DCE by Hauber et al<sup>21</sup> included here demonstrated that people with T2D preferred OADs that were not associated with stomach upset (although this was less important to them than other issues such as glycemic control and weight gain).

In many of the studies that reported on hypoglycemia and its impact on medication-taking indicators identified in this review, hypoglycemia was included in a broader category of attributes.<sup>16,25,26</sup> Nevertheless, where it was specifically described, symptoms of hypoglycemia appeared to affect the likelihood of treatment initiation,<sup>15</sup> adherence,<sup>18,21</sup> and discontinuation.<sup>23,24</sup> The negative impact of hypoglycemia on medication-taking indicators might be explained by its association with poorer HRQoL: hypoglycemia has been reported to detrimentally affect various aspects of well-being and functioning, as well as relationships and work performance.<sup>52,53</sup> In addition, people with T2D who experience hypoglycemia report worse treatment satisfaction compared with individuals without hypoglycemia.<sup>54</sup> The presence of symptoms has also been shown to be associated with increased rates of fear of hypoglycemia (FOH),<sup>54</sup> which can itself have a negative impact on HRQoL, particularly with respect to psychosocial functioning, daily living, and sleep quality.<sup>55</sup>

The studies identified also indicated that dose frequency and regimen complexity affected indicators of medication-taking. This is consistent with other evidence clearly demonstrating that people with T2D prefer medications with a lower dosing frequency<sup>31,32,56</sup> and that less frequent dosing is associated with better medication adherence.<sup>57,58</sup> Similarly, treatment adherence has been reported to decrease as the regimen complexity increases.<sup>59</sup>

The current review is subject to some limitations. Even though a robust and reproducible protocol was used to identify studies, relevant research may have been published that were missed and some could have been published outside the date cut-off. In addition, we employed a two-stage approach for reviewing the search results such that at the first stage, the decision to include or exclude a publication is made based on review of the title/abstract and not on a comprehensive review of the full text of the article. It is, therefore, possible that potentially relevant studies were excluded at this stage due to lack of detail in the title or abstract.

After full-text review of potentially eligible studies, a decision was made to exclude those focused on insulin for reasons outlined in the methods. Medication-taking indicators in insulin-treated individuals are influenced by a broad range of concepts, many of which were outside of the scope of this review. However, insulin is an important treatment option for people with T2D and there is evidence that insulin treatment-related attributes do impact medication-taking behaviors in these individuals, suggesting that an in-depth review of these relationships would be of interest.<sup>60–62</sup>



Another limitation is that it was often difficult to interpret exactly what attributes were being referred to within each study, which was particularly true of qualitative studies. For example, an individual mentioning regimen complexity could have been referring to a number of aspects including the complexity of the regimen itself, the device, or method of administration; interference with daily activities; or psychosocial issues, such as stigma. Similarly, attributes were sometimes described under what appeared to be an “umbrella” term wherein multiple factors were included under a broader category. This was particularly true for the attributes of GI AEs and hypoglycemia. For example, in the study by Chen et al, one of the attributes put to study participants was “worries about AEs of injection therapy, such as hypoglycemia and weight gain.” These results are included in the review because specific issues were explicitly mentioned, but individuals agreeing with this catch-all statement will obviously be experiencing a range of AEs that are not restricted to the examples provided. Similarly, in their study, Spain et al included an attribute of “burden/inconvenience”, which again could comprise a broad range of issues. This category was described in the study methods as including aspects of treatment such as dose frequency, and so was included in the current review.

Six of the included studies also evaluated AEs as a general treatment attribute without specifying their nature. In these instances, data were not summarized in the review as we were only interested in specific AEs such as those associated with GI function, hypoglycemia, and weight gain. Clearly, AEs are an issue in general and are a major influence on medication-taking behaviors, but the evidence base would have been richer had the nature of AEs been more explicit.

One major limitation of the evidence base is that we cannot readily compare or combine findings across studies or across different attributes, and it is not possible to reach any conclusions regarding which, if any, attribute has more influence over another on medication-taking behaviors. This is because studies varied considerably with respect to populations, drugs evaluated, stage of treatment journey or disease, and designs. Furthermore, study numbers reporting findings for specific attributes at different parts of the treatment journey were often low.

Another important consideration is that the attributes that influence behaviors may vary according to different PwD characteristics, attitudes, and previous treatment or disease experiences. For example, with respect to weight, there is evidence that, in general, women are more dissatisfied with their weight<sup>63</sup> and so may value weight loss more highly than men. In addition, people with overweight or obesity may be more likely to respond that weight loss is an important treatment attribute influencing their behavior, while those of a healthier weight are less likely to do so. Indeed, in the DCE by Hauber et al,<sup>21</sup> it was found that participants who had experienced weight gain with their current medication would be more likely to indicate that medication attributes would negatively affect adherence. Polonsky et al also demonstrated that users of injectable medications with worse HRQoL were more willing to initiate a hypothetical QW injectable if it helped avoid weight gain, reduce blood glucose spikes, or lower risk of hypoglycemia compared with individuals who had better HRQoL.<sup>15</sup> Users of OADs who viewed blood glucose control as more problematic were also more willing to initiate a new QW injectable therapy compared with individuals with whose glycemia was well managed.<sup>15</sup> It could also be that previous experience of hypoglycemia or FOH may lead to the behaviors of people with T2D being more heavily influenced by hypoglycemia as a treatment-related attribute. For example, it has been reported that insulin dose omission or mistiming occur more frequently among people with T2D who have previously experienced hypoglycemia.<sup>64</sup>

The different methods by which participants were presented attributes could also have influenced study findings. In some cases, studies used questionnaires that presented a list of attributes from which participants picked those that were relevant to them with respect to any medication-taking behavior. Often, the list of attributes was informed by previous qualitative research or literature searches, but it is possible these lists may not have included all factors important or relevant to the chosen study population. Indeed, the lists of attributes presented, or the description or wording used, varied from one study to another. It is possible that the different phrasing across studies, wherein similar attributes were framed as concerns/barriers to medication taking in some studies but as motivations in others, may have influenced participant’s perceptions (eg weight gain or loss are flip sides of the same attribute, but people with T2D may feel more strongly about one over the other).

Finally, it should be noted that many of the studies do not evaluate the impact of treatment-related attributes on medication-taking behaviors directly and rather use proxy measures such as, for example, willingness to take a medication or the likelihood of missing or skipping doses.<sup>15,21</sup> Furthermore, in several studies, participants indicate

that treatment-related attributes influence a hypothetical behavior; for example, they might suggest that an attribute is a motivator or barrier to adherence but the prospective association between that attribute and actual adherence at a later time point is not measured. Studies designed to prospectively evaluate this relationship are, therefore, warranted.

## Conclusions

This review evaluated research in which people with T2D directly indicated the treatment-related attributes associated with their decision to initiate a medication, to stay on a medication, or to discontinue treatment. The included studies represent a consolidation of research on this topic and are a useful resource. Several treatment-related attributes including glycemic efficacy, effect on weight, hypoglycemia, GI AEs, dose frequency, and regimen complexity all appeared to play a role in how people with T2D took their medication at different points of the treatment journey.

The findings from this review may contribute to a greater understanding of the attributes that impact behaviors and could assist HCPs and people with T2D to make more informed treatment decisions. Each PwD will likely have a unique set of beliefs and attitudes towards different medications, and it is advisable that HCPs should routinely inquire about such perceptions and take them into account when making any treatment recommendations such that medications are chosen that individual PwD are comfortable initiating and persisting with for longer periods of time and that show efficacy in achieving standard-of-care treatment outcomes. In addition, the insights from this review may help to develop strategies and interventions for the support of medication taking that better meet the needs of PwD.

## Data Sharing Statement

Data sharing is not applicable to this article as, since this is a review, no datasets were generated or analyzed.

## Ethics Approval and Informed Consent

This article is a review and analysis of previously published studies and does not include any new studies on human or animal subjects performed by any of the authors.

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## Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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