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A systematic review

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REVIEW

Adherence to newer second-line oral antidiabetic drugs among people with type 2 diabetes—A systematic review

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Abstract

The adherence to oral antidiabetic drugs (OADs) among people with type 2 diabetes (T2D) is suboptimal. However, new OADs have been marketed within the last 10 years. As these new drugs differ in mechanism of action, treatment complexity, and side effects, they may influence adherence. Thus, the aim of this study was to assess the adherence to newer second-line OADs, defined as drugs marketed in 2012–2022, among people with T2D. A systematic review was performed in CINAHL, Cochrane Trials, Embase, PubMed, PsycINFO, and Scopus. Articles were included if they were original research of adherence to newer second-line OADs and reported objective adherence quantification. The quality of the articles was assessed using JBI's critical appraisal tools. The overall findings were reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and summarized in a narrative synthesis. All seven included articles were European retrospective cohort studies investigating alogliptin, canagliflozin, dapagliflozin, empagliflozin, and unspecified types of SGLT2i. Treatment discontinuation and medication possession ratio (MPR) were the most frequently reported adherence quantification measures. Within the first 12 months of treatment, 29%–44% of subjects on SGLT2i discontinued the treatment. In terms of MPR, 61.7%–94.9% of subjects on either alogliptin, canagliflozin, dapagliflozin, empagliflozin or an unspecified SGLT2i were adherent. The two investigated adherence quantification measures, treatment discontinuation and MPR, suggest that adherence to the newer second-line OADs may be better than that of older OADs. However, a study directly comparing older and newer OADs should be done to verify this.

KEYWORDS
adherence, oral antidiabetic drug, review, type 2 diabetes

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1 | INTRODUCTION

In 2021, approximately 536 million people aged 20–79 had a diagnosis of diabetes. The vast majority of these people had a diagnosis of type 2 diabetes (T2D).[1] T2D is characterized by a dysregulation of the blood glucose, resulting in hyperglycemia, which over time may lead to long-term complications such as cardiovascular disease, nephropathy, and neuropathy. Therefore, the aim of the antidiabetic treatment is to keep the blood glucose within the normal range.[2] The recommended first-line treatment, according to the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), is lifestyle modification combined with metformin treatment.[2] When the first-line treatment fails to keep the blood glucose within the normal range due to disease progression, a second-line drug is added to the treatment regimen.[2] The recommended second-line treatment is either a sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl peptidase 4 inhibitor (DPP-4i), glucagon-like peptide 1 receptor agonist (GLP-1 RA), sodium-glucose cotransporter 2 inhibitor (SGLT2i) or basal insulin.[2]

Potential comorbidities and the patient's preferences should be considered when choosing which second-line antidiabetic drug to add to the treatment regimen.[2] The patient's preference regarding the route of administration, side effects, and medication complexity may influence the patient's treatment adherence, as these are all potential barriers to adherence.[3–5] As all five recommended non-insulin second-line antidiabetic drug classes are available in an oral form, it is possible for most patients with T2D to have a treatment regimen consisting entirely of oral antidiabetic drugs (OADs).

The adherence to OADs among people with T2D has previously been investigated using objective adherence quantification measures and reported in systematic reviews and meta-analysis.[6–10] Cramer,[6] Krass et al.,[7] Iglay et al.,[8] and Evans et al.[10] all found that the adherence to OADs is suboptimal. Furthermore, Evans et al.[10] and McGovern et al.[9] found that the adherence between drug classes varied significantly. In 2012, the first drug of an entirely new drug class, the SGLT2is, was approved by the European Medicines Agency (EMA).[11,12] Since 2012, several new OADs, used as second-line treatment, have been marketed. These are the SGLT2is canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, the DPP-4i alogliptin, and the GLP-1 RA oral semaglutide.[13] These new drugs differ in mechanism of action, treatment complexity, and side effects, which all may influence the adherence. The aim of this study was to assess the adherence to newer second-line OADs, defined as drugs marketed within the last 10 years (2012–2022), among people with T2D.

2 | MATERIALS AND METHODS

A systematic literature search was performed to identify studies, which investigated the adherence to newer second-line OADs. The search was performed on the 12 and 13 July 2022 and included articles published from 2012 to the search date. The protocol of the systematic literature search was preregistered on PROSPERO (registration ID: CRD42022344503).

2.1 | Search strategy

The literature search was performed as a block search consisting of the three blocks "T2D", "OAD", and "Adherence". Each block consisted of synonyms, near-synonyms, acronyms, and relevant index terms. All terms were searched for in the title and abstract of the articles as free text. The literature search was performed in six databases: CINAHL, Cochrane Trials, Embase, PubMed, PsycINFO, and Scopus. The search string was adapted to each database (the full search string of each database is shown in Data S1). Furthermore, the search was restricted to articles written in English language only.

2.2 | Study selection

The articles retrieved from each database were pooled and duplicates were removed. Following, articles were screened based on the title and abstract, and the remaining articles underwent full-text screening. Articles were included if (1) the study subjects received metformin and one type of a newer second-line OAD, (2) the study investigated adherence to a newer second-line OAD, (3) the article was available in full text, and (4) the article was original research. Studies focusing on subjects with comorbidities or were set during special circumstances were excluded from the study, thereby obtaining a relatively homogeneous study group. Moreover, as subjects with comorbidities in general take more medication and the choice of antidiabetic medication may be conditioned by recommendations, adherence may be influenced. Likewise, the subjects' behavior regarding treatment adherence might be different during special circumstances compared to everyday settings and could potentially also influence adherence. These potential confounding variables were minimized by excluding articles if (1) the study subjects were younger than 18 years, (2) the study subjects had a diagnosis of diabetes other than T2D, (3) the inclusion criteria of the study included comorbidities, and (4) the study was set during special circumstances, such as Ramadan or the COVID-19 pandemic. The selection of studies was conducted and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA)[14] using the software Rayyan, developed by Ouzzani et al.,[15] to record the decision for each article.

2.3 | Quality assessment

The quality of the included articles was assessed individually using JBI's critical appraisal tools.[16] JBI's critical appraisal tools was chosen, as it has the broadest range of checklists for different study designs[17] and therefore can handle that no restriction was made for

the study design. The specific checklist used to assess each included article was chosen in accordance with the study design reported in the article. If the study design was not reported, the authors assessed and determined the design. Each included article was given a score based on the scoring system reported by Melo et al.[18] A score of ≥70% was considered as a low risk of bias, a score between 50% and 69% as a moderate risk of bias, and a score of <49% as a high risk of bias.[18]

2.4 | Data extraction and data synthesis

The information extracted from each included article was the trial design, sample size, demographics, clinical information, i.e., glycated hemoglobin (HbA1c), body mass index (BMI), and duration of T2D, treatment regimen, the adherence level to newer second-line OAD, and the adherence quantification measure used. The type of adherence quantification measure was not restricted, as both the adherence level within and between the drug classes was grouped by the adherence quantification measure for comparison. In studies reporting the adherence to different types of OADs, the adherence quantification measure of a subgroup was only considered if the studied treatment was metformin and an OAD, marketed after 2012. The extracted information is presented in tables and the adherence to newer second-line OADs are visualized in figures. The

overall findings of this systematic review are summarized in a narrative synthesis.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[19] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[20]

3 | RESULTS

A total of 14948 articles were identified through the systematic literature search. Seven articles met the criteria and were thus included as the final sample. The study selection process is reported in the PRISMA 2020 flow diagram shown in Figure 1.

3.1 | Study characteristics

The characteristics of the included articles and study populations of these is reported in Table 1. All seven included studies were

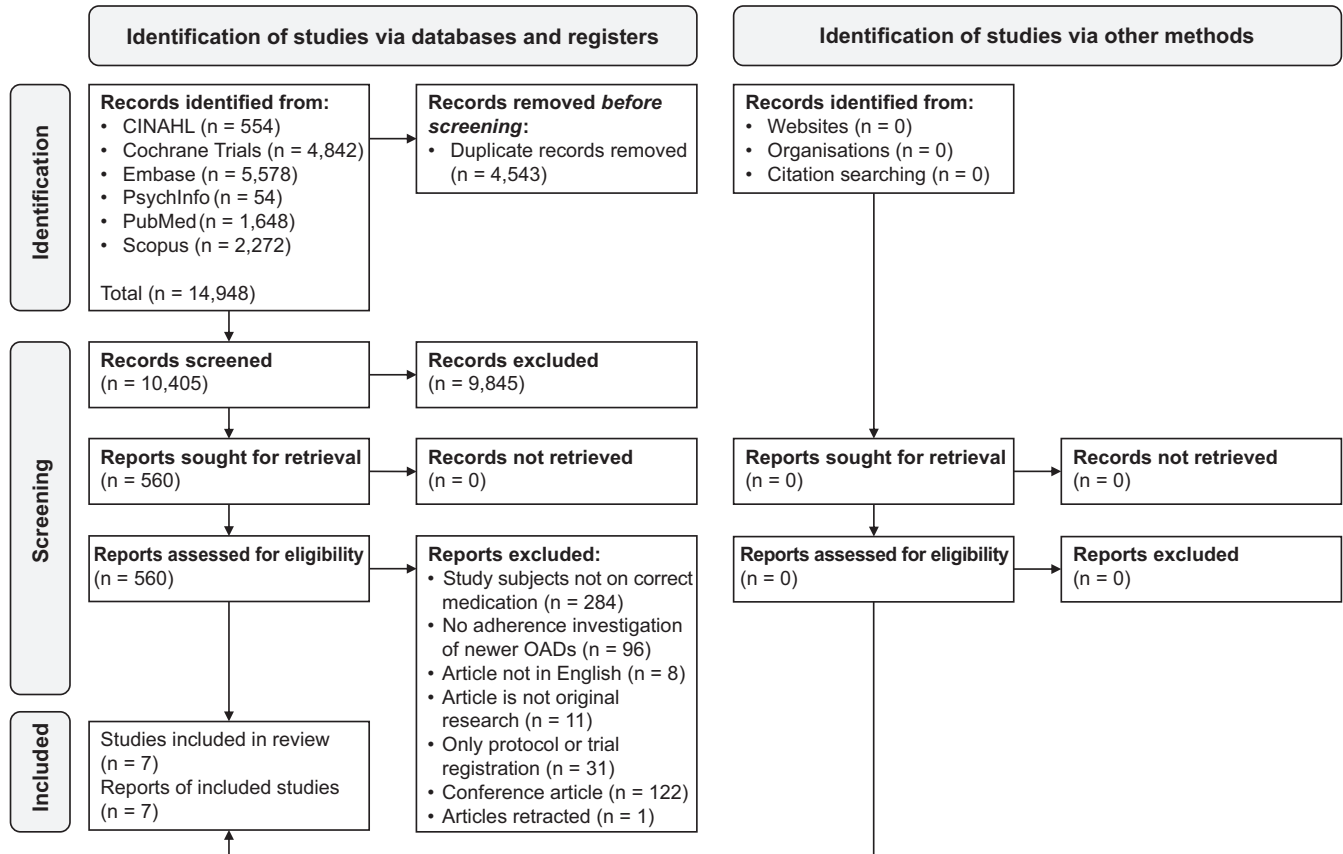FIGURE 1 PRISMA 2020 flow diagram[14] of the study selection process.

TABLE 1 Overview of the included articles and the characteristics of the study population.

Author, Year	Country	Study type	Data source	Duration and time of trial	Second-line OAD	Sample size	Age	Sex	T2D Duration	HbA1c
Gordon et al.[21]	UK	Cohort study	The Clinical Practice Research Datalink (CPRD) database.	Duration: Up to 365 days Time: 2008–2016	SGLT2i (unspecified)	232	Not reported	Not reported	Not reported	Not reported
Jermendy et al.[24]	Hungary	Cohort study	The National Institute of Health Insurance Fund Management database.	Duration: Up to 2 years Time: 2014–2017	SGLT2i (dapagliflozin or empagliflozin)	2603	Mean: 59.5 years SD: 9.4 years	Males: 50.5%	Not reported	Not reported
Rea et al.[25]	Lombardy, Italy	Cohort study	The Healthcare Utilization databases of Lombardy.	Duration: 1 year Time: 2007–2015	SGLT2i (canagliflozin, dapagliflozin or empagliflozin)	1276	69.5% was 40–64 years and 30.5% was ≥65 years.	Males: 62.3%	Not reported	Not reported
Romagnoli et al.[22]	Pescara, Italy	Cohort study	The administrative database of the pharmacy of the Hospital of Pescara, Italy.	Duration: Up to 3 years Time: 2011–2019	SGLT2i (unspecified)	757	Median: 65 years Min-Max: 33–90 years	Males: 60%	Not reported	Not reported
Strain et al.[23]	UK	Cohort study	The Clinical Practice Research Datalink (CPRD) database.	Duration: Up to 2 years Time: 2012–2016	SGLT2i (unspecified)	490	Mean: 56.25 years SD: 9.80 years	Males: 56.1%	Mean: 4.21 years SD: 3.01 years	Mean: 8.38% SD: 0.80%
Vlacho et al.[26]	Catalonia, Spain	Cohort study	The SIDIAP (Information System for the Development of Research in Primary Care) database.	Duration: Up to 24 months Time: 2010–2017	DPP4i (alogliptin) SGLT2i (canagliflozin, dapagliflozin or empagliflozin)	Alogliptin: 22 Dapagliflozin: 539 Empagliflozin: 501 Canagliflozin: 175	Alogliptin: Not reported. SGLT2is: Mean: 60.5 years SD: 11.1 years	Alogliptin: Not reported. SGLT2is: Males: 56.5%	Alogliptin: Not reported SGLT2is: Mean: 7.89 years SD: 6.67 years	Alogliptin: Not reported SGLT2is: Mean: 8.77% SD: 1.49%
Wilding et al.[27]	UK	Cohort study	Clinical Practice Research Datalink (CPRD) database.	Duration: Up to 18 months Time: 2013–2016	SGLT2i (canagliflozin, dapagliflozin or empagliflozin)	441	Mean: 55.05 years SD: 10.14 years	Males: 60.3%	Median: 3.30 years IQR: 1.47–5.55	Mean: 9.07% SD: 1.58%

TABLE 2 Quality assessment of the included articles based on JBI's critical appraisal tools.[16]

Article	JBI's critical appraisal checklist questions for cohort studies											Score	Risk of bias
	1	2	3	4	5	6	7	8	9	10	11		
Gordon et al.[21]	+	+	+	+	+	NA	+	+	+	+	+	10/10 100%	Low
Jermendy et al.[24]	U	+	+	+	−	NA	+	+	−	−	+	3/10 30%	High
Rea et al.[25]	+	+	+	+	+	NA	+	+	−	U	+	8/10 80%	Low
Romagnoli et al.[22]	+	+	+	U	−	NA	+	+	−	+	+	5/10 50%	Moderate
Strain et al.[23]	+	+	+	+	+	NA	+	+	−	−	+	6/10 60%	Moderate
Vlacho et al.[26]	+	+	+	+	+	NA	+	+	+	U	+	9/10 90%	Low
Wilding et al.[27]	+	+	+	+	+	NA	+	+	U	−	+	7/10 70%	Low

Note: For each question of the appraisal checklist for cohort studies, the answer is reported, and the total score is used to assess the risk of bias. A score of ≥70% was considered as a low risk of bias, a score between 50%–69% as moderate risk of bias, and a score of <49% as high risk of bias, as reported by Melo et al.[18]

Abbreviations: +: yes; −: no; NA, not applicable; U, unclear.

retrospective cohort studies using data from European countries (Hungary, Italy, Spain, and the United Kingdom) to determine the adherence level. The second-line OADs investigated in these studies were the DPP4i alogliptin and the SGLT2is canagliflozin, dapagliflozin, and empagliflozin. Furthermore, Gordon et al.,[21] Romagnoli et al.,[22] and Strain et al.[23] investigated adherence to SGLT2is, but did not report the type of SGLT2is being investigated.

3.2 | Quality assessment

As all included studies were cohort studies, and the quality assessment was based on JBI's critical appraisal checklist for cohort studies. The quality assessment of each included article is reported in Table 2.

All but one of the included articles were evaluated to have a low to moderate risk of bias based on JBI's critical appraisal tools for cohort studies (Table 2). In contrast, the risk of bias in the article by Jermendy et al.[24] was assessed to be high. The assessment of a high risk of bias in the article of Jermendy et al.[24] is a result of that (1) it is unclear whether the study groups have similar characteristics, (2) no strategies were used to deal with confounding factors, and (3) the reasons of loss to follow-up were not explored and methods to consider incomplete follow-up was not used in the analysis.

3.3 | Adherence to second-line oral antidiabetic drugs

3.3.1 | Measurement methods

In the included articles, the objective measures to quantify adherence was (1) treatment discontinuation, (2) medication possession

TABLE 3 Overview of the measurement methods used to ascertain the adherence to second-line OADs in the included articles.

Article	Measurement method
Gordon et al.[21]	MPR
Jermendy et al.[24]	Discontinued[a] subjects at 12 months
Rea et al.[25]	Discontinued[b] subjects at 12 months
Romagnoli et al.[22]	RDD/PDD
Strain et al.[23]	MPR + Discontinued[c] subjects at 6 and 12 months
Vlacho et al.[26]	MPR + Discontinued[a] subjects at 6, 12, and 24 months
Wilding et al.[27]	Discontinued[d] subjects at 6, 12, and 18 months

Note: Discontinuation was defined as a period without treatment of a: ≥90 days, b: ≥60 days, c: not reported, and d: ≥184 days.

Abbreviations: MPR, medication possession ratio; PDD, prescribed daily dose; RDD, received daily dose.

ratio (MPR), and (3) the ratio between the received daily dose (RDD) and prescribed daily dose (PDD). The reported measurement methods to ascertain adherence to second-line OADs in the included articles are shown in Table 3.

A total of five articles[23-27] reported the percentage of subjects discontinuing treatment with a second-line OAD at given time points after treatment initiation. However, the duration of the treatment-free period used to define treatment discontinuation, varied across the studies, spanning from 60 to 184 days[23-27] (Table 3). Treatment discontinuation was defined as a change in the type of OAD by Jermendy et al.,[24] Rea et al.,[25] Strain et al.,[23] and Vlacho et al.,[26] whereas Wilding et al.[27] also included treatment intensification as treatment discontinuation.

MPR is defined as the ratio between the number of days a patient is supplied with the given medication and the number of days between each medication refill over a given time span.[28] It expresses the percentage of time that a subject has the medication available[28] and is, thus, a proxy for treatment adherence. The commonly used definition of treatment adherence, in terms of MPR, is MPR ≥80%.[28] The percentage of adherent subjects, in terms of MPR, was reported in three of the articles.[21,23,26]

3.3.2 | Treatment discontinuation

The five studies[23–27] reporting treatment discontinuation solely focused on SGLT2is but did not report the type of SGLT2i. Thus, a comparison between the different SGLT2i types in terms of discontinuation was not possible. The percentage of subjects discontinuing SGLT2is as a second-line treatment within the first 24 months after treatment initiation are shown in Figure 2.

The percentage of discontinued subjects 12 months after treatment initiation was reported by all five studies.[23–27] Similar percentages of discontinued subjects at 12 months, approximately 30%, were reported by all except Jermendy et al.[24] that reported a higher percentage of treatment discontinuation of 44% (Figure 2). Strain et al.[23] and Wilding et al.[27] reported treatment discontinuation based on data from the same database.

The course of the cumulated percentage of subjects discontinuing treatment are relatively similar across the five studies with a tendency of decreasing percentages of subjects discontinuing the treatment. A statistical test was not performed to compare the slopes, as a such test would have insufficient power due to the low number of samples.

3.3.3 | Medication possession ratio

The percentage of adherent subjects, defined as subjects with an MPR ≥80%, by type and class of drug are shown in Figure 3. The reported percentage of adherent subjects ranged from 61.7% to 94.9%. The lowest percentage of adherent subjects was reported in a group treated with empagliflozin[26] and the highest percentage was reported in subjects treated with an unspecified SGLT2i.[23]

The DPP4i alogliptin and the SGLT2is canagliflozin, dapagliflozin, and empagliflozin were compared by Vlacho et al.[26] The percentage of subjects, which were adherent to alogliptin (72.7%) was comparable to that of canagliflozin (73.7%) and dapagliflozin (71.7%).[26] However, the percentage of subjects, adherent to alogliptin, was based on 22 subjects.[26] Among the three types of SGLT2i, the highest percentage of adherent subjects was reported in the group treated with canagliflozin (73.7%), followed by dapagliflozin (71.7%), and the lowest percentage of adherent subjects for empagliflozin
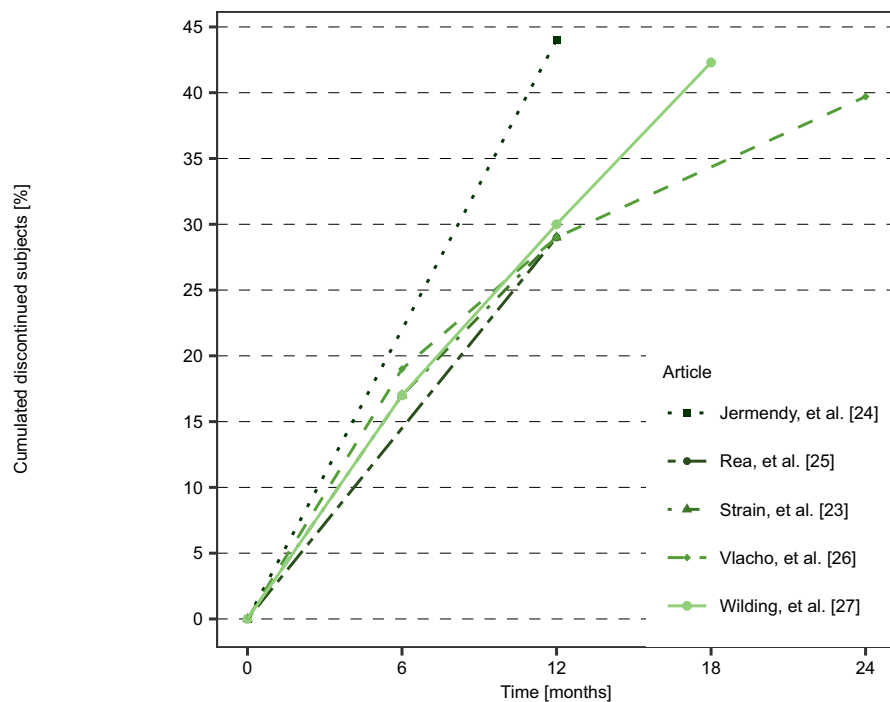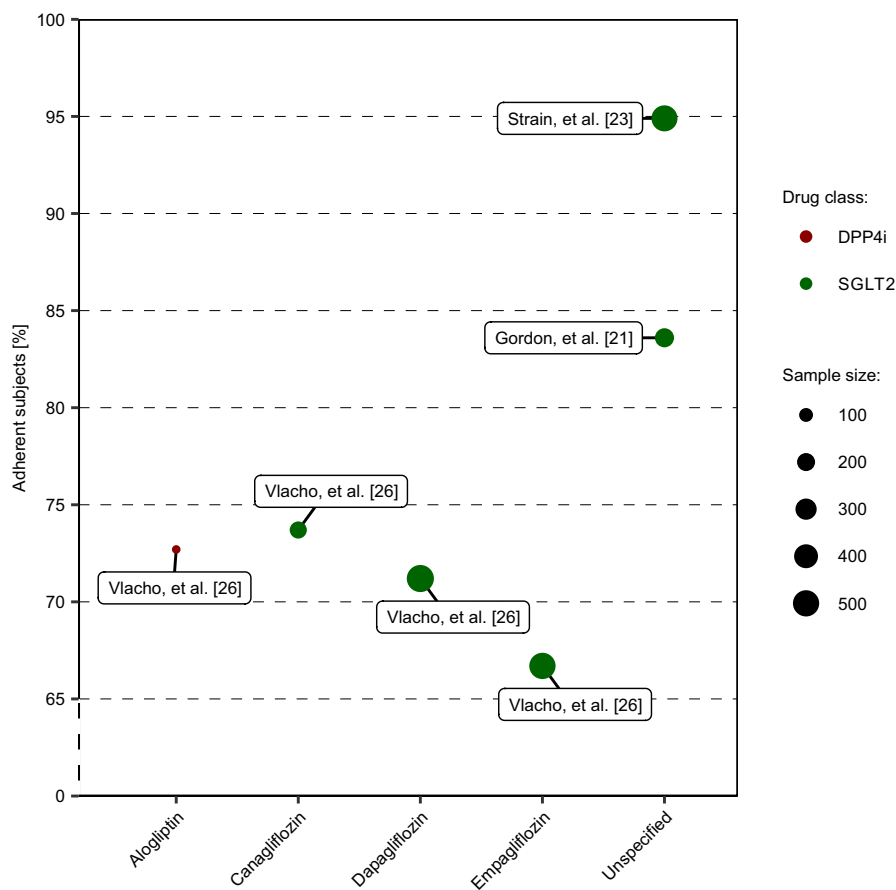

Article		6	12	18	24
Wilding, et al. [27]	441	17%	30%	42%	-
Vlacho, et al. [26]	2117	19%	29%	-	40%
Strain, et al. [23]	490	17%	29%	-	-
Rea, et al. [25]	1276	-	29%	-	-
Jermendy, et al. [24]	2603	-	44%	-	-

FIGURE 2 Cumulated discontinuation of SGLT2i as second-line treatment among people with T2D on background metformin. The table shows the number of subjects initiating the treatment and the cumulated percentage of discontinued subjects at 6, 12, 18, and 24 months after treatment initiation. The hyphen (–) indicates that no discontinuation percentage was reported in the article of the study at the given time.

for the newer second-line OADs investigated in the present systematic review was 29%–44%. However, as no direct comparison were made between the newer and older second-line OADs, a final conclusion cannot be drawn.

In this systematic review, the OAD with the highest percentage of adherent subjects in terms of MPR was canagliflozin when compared to that of alogliptin, dapagliflozin, and empagliflozin. These four OADs differ in attributes such as associated side effects and dosing requirements, which may influence the adherence. The patients' preferences regarding the attributes of newer OADs, were investigated by Savarese et al.[30] in a survey of 553 people with T2D from the United States. In the survey, the patients ranked risk of genital infections highest, followed by reduction of body weight, dosing conditions involving fasting and food restrictions, risk of vomiting, and risk reduction of cardio vascular death.[30] SGLT2is i.e., canagliflozin, dapagliflozin, and empagliflozin are associated with an increased risk of genital infection,[31,32] whereas DPP4is, i.e., alogliptin are not.[32] The SGLT2is are, nonetheless, associated with weight loss[32] and reduced risk of cardiovascular complications[31] while the DPP4is might slightly increase body weight[32] and have no effect on cardiovascular complications.[31] Neither DPP4is nor SGLT2is have an increased risk of gastrointestinal side effects.[32] The method of administration differs in complexity, also within the class of SGLT2i. Alogliptin, dapagliflozin and empagliflozin have the least complex method of administration, as these can be taken with or without food,[12,33,34] whereas canagliflozin should be administered prior to the first meal of the day.[35] Despite that canagliflozin, as an SGLT2i, is associated with an increased risk of genital infection, which according to the survey by Savarese et al.[30] is ranked as the biggest consideration, and has the most complex administration method of the three SGLT2is, it had the highest reported percentage of adherent patients. However, these adherence data was all reported by Vlacho et al.[26] and the sample sizes were relatively small. Thus, more data is needed to investigate the influence of potential adherence barriers on treatment adherence.

The adherence was quantified based on data from pharmacy claims and registries in the included articles. As it is not possible to verify whether a subject actually takes the prescribed medication, the prescribed dosage, and abides by the prescribed method of administration, the adherence might be overestimated. Furthermore, overlapping medication supply is not taken into consideration in the calculation of MPR, which can also result in an overestimation. However, adherence quantification measures based on data from pharmacy claims and registries can be used as proxies for adherence and are commonly used methods to quantify adherence.[28]

In the included studies, the most reported adherence quantification measures were MPR and treatment discontinuation. Thus, it was possible to investigate two distinct aspects of treatment adherence, namely how long the subjects remained on the treatment and to what degree the subjects took the medication while on the treatment. However, both adherence quantification measures were defined differently across the included articles. The reported treatment discontinuation varied across the studies in terms of when a subject was considered as discontinued on the treatment and how loss to follow-up was managed. Similarly, the reported MPR was calculated over different durations across the studies and differed in terms of whether loss to follow-up was considered in the calculations. Thus, the reported adherence quantification measures may not be directly comparable across the studies but provides an indication for the adherence level.

This systematic review is based on a systematic literature search, which was conducted in a highly systematic way in seven different databases to ensure all relevant articles were retrieved. The design of the systematic literature search was made with input from research librarians at Aalborg University Library and at the Medical Library of Aalborg University Hospital to ensure a high quality of the literature search.

The main limitation of this systematic review is the relatively few included studies. Thus, no statistical tests were performed, as power would be too low due to the low number of studies. Instead, the conclusions have been moderated to reflect the low number of included studies. Additionally, all the included studies were conducted in European countries, which may introduce a bias, as the diversity of the study population is limited and might not be representative outside of Europe.

5 | CONCLUSIONS

The reported findings of SGLT2i discontinuation over time from treatment initiation had a decreasing tendency that might indicate that the treatment discontinuation risk is greatest immediately after initiation. Across the included studies, between 29% and 44% of subjects on SGLT2i discontinued their treatment within the first 12 months of treatment initiation. In terms of MPR, 61.7%–94.9% of subjects treated with either alogliptin, canagliflozin, dapagliflozin, empagliflozin or an unspecified type of SGLT2i were adherent. Overall, both adherence quantification measures indicate that the adherence to the newer second-line OADs may be better than that of older OADs but should be verified with a study directly comparing older and newer OADs.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors Dethlefsen, Holdt-Caspersen, and Jensen are employees of Novo Nordisk and hold shares herein. Peter Vestergaard is the Head of Research at Steno Diabetes Center North Denmark funded by the Novo Nordisk Foundation.

DATA AVAILABILITY STATEMENT

Data can be made available upon request from the corresponding author.

ETHICS STATEMENT

Approval from an ethics committee was not necessary, as this was not a clinical trial.

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REFERENCES

1. Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119. doi:10.1016/j.diabres.2021.109119
2. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2022;45(11):2753-2786. doi:10.2337/dci22-0034
3. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1306. doi:10.2147/PPA.S106821
4. Brundisini F, Vanstone M, Hulan D, DeJean D, Giacomini M. Type 2 diabetes patients' and providers' differing perspectives on medication nonadherence: a qualitative meta-synthesis. *BMC Health Serv Res*. 2015;15(1):1-23. doi:10.1186/s12913-015-1174-8
5. Lee DSU, Lee H. Adherence and persistence rates of major antidiabetic medications: a review. *Diabetol Metab Syndr*. 2022;14(1):12. doi:10.1186/s13098-022-00785-1
6. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care*. 2004;27(5):1218-1224. doi:10.2337/diacare.27.5.1218
7. Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. *Diabet Med*. 2015;32(6):725-737. doi:10.1111/dme.12651
8. Iglay K, Cartier SE, Rosen VM, et al. Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral antihyperglycemic agents in type 2 diabetes. *Curr Med Res Opin*. 2015;31(7):1283-1296. doi:10.1185/03007995.2015.1053048
9. McGovern A, Tippu Z, Hinton W, Munro N, Whyte M, de Lusignan S. Comparison of medication adherence and persistence in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2018;20(4):1040-1043. doi:10.1111/dom.13160
10. Evans M, Engberg S, Faurby M, Fernandes J, Hudson P, Polonsky W. Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: a systematic literature review. *Diabetes Obes Metab*. 2022;24(3):377-390. doi:10.1111/dom.14603
11. Plosker GL. Dapagliflozin: a review of its use in type 2 diabetes mellitus. *Drugs*. 2012;72:2289-2312. doi:10.2165/11209910-000000000-00000
12. European Medicines Agency. Forxiga: EPAR—product information. 2023. Accessed February 1, 2023. https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf
13. Dahlén AD, Dashi G, Maslov I, et al. Trends in antidiabetic drug discovery: FDA approved drugs, new drugs in clinical trials and global sales. *Front Pharmacol*. 2022;12:807548. doi:10.3389/fphar.2021.807548
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev*. 2021;10(1):1-11. doi:10.1186/s13643-021-01626-4
15. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:1-10. doi:10.1186/s13643-016-0384-4
16. Moola S, Munn Z, Tufanaru C, et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, eds. *JBI manual for evidence synthesis*. JBI; 2020.
17. Ma L-L, Wang Y-Y, Yang Z-H, Huang D, Weng H, Zeng X-T. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? *Mil Med Res*. 2020;7:1-11. doi:10.1186/s40779-20-00238-8
18. Melo G, Dutra KL, Rodrigues Filho R, et al. Association between psychotropic medications and presence of sleep bruxism: a systematic review. *J Oral Rehabil*. 2018;45(7):545-554. doi:10.1111/joor.12633
19. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Res*. 2018;46(D1):D1091-D1106. doi:10.1093/nar/gkx1121
20. Alexander SP, Fabbro D, Kelly E, et al. The concise guide to PHARMACOLOGY 2023/24: enzymes. *Br J Pharmacol*. 2023;180:S289-S373. doi:10.1111/bph.16181
21. Gordon J, McEwan P, Idris I, Evans M, Puelles J. Treatment choice, medication adherence and glycemic efficacy in people with type 2 diabetes: a UK clinical practice database study. *BMJ Open Diabetes Res Care*. 2018;6(1):e000512. doi:10.1136/bmjdrc-2018-000512
22. Romagnoli A, Santoleri F, Costantini A. Drug utilisation pattern over 3 years in the real-world treatment of type II diabetes. *Int J Clin Pract*. 2021;75(6):e14120. doi:10.1111/ijcp.14120
23. Strain WD, Tsang C, Hurst M, et al. What next after metformin in type 2 diabetes? Selecting the right drug for the right patient. *Diabetes Therapy*. 2020;11(6):1381-1395. doi:10.1007/s13300-020-00834-w
24. Jermendy G, Kiss Z, Rokszin G, Abonyi-Tóth Z, Wittmann I, Kempler P. Persistence to treatment with novel antidiabetic drugs (dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists) in people with type 2 diabetes: a Nationwide cohort study. *Diabetes Therapy*. 2018;9(5):2133-2141. doi:10.1007/s13300-018-0483-4
25. Rea F, Ciardullo S, Savaré L, Perseghin G, Corrao G. Comparing medication persistence among patients with type 2 diabetes using sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists in real-world setting. *Diabetes Res Clin Pract*. 2021;180. doi:10.1016/j.diabres.2021.109035
26. Vlacho B, Mata-Cases M, Mundet-Tudurí X, et al. Analysis of the adherence and safety of second oral glucose-lowering

therapy in routine practice from the mediterranean area: a retrospective cohort study. *Front Endocrinol*. 2021;12. doi:10.3389/fendo.2021.708372

27. Wilding J, Godec T, Khunti K, et al. Changes in HbA1c and weight, and treatment persistence, over the 18 months following initiation of second-line therapy in patients with type 2 diabetes: results from the United Kingdom Clinical Practice Research Datalink. *BMC Med*. 2018;16(1). doi:10.1186/s12916-018-1085-8

28. Clifford S, Perez-Nieves M, Skalicky AM, Reaney M, Coyne KS. A systematic literature review of methodologies used to assess medication adherence in patients with diabetes. *Curr Med Res Opin*. 2014;30(6):1071-1085. doi:10.1185/03007995.2014.884491

29. Odegard PS, Capoccia K. Medication taking and diabetes. *Diabetes Educ*. 2007;33(6):1014-1029. doi:10.1177/0145721707308407

30. Savarese G, Sharma A, Pang C, Wood R, Soleymanlou N. Patient preferences for newer oral therapies in type 2 diabetes. *Int J Cardiol*. 2023;371:526-532. doi:10.1016/j.ijcard.2022.09.009

31. Sim R, Chong CW, Loganadan NK, et al. Comparative effectiveness of cardiovascular, renal and safety outcomes of second-line antidiabetic drugs use in people with type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. *Diabet Med*. 2022;39(3):e14780. doi:10.1111/dme.14780

32. Shi Q, Nong K, Vandvik PO, et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ*. 2023;381:e074068. doi:10.1136/bmj-2022-074068

33. European Medicines Agency. Jardiance: EPAR—product information. 2022. [Online]. https://www.ema.europa.eu/en/documents/product-information/jardiance-epar-product-information_en.pdf

34. European Medicines Agency. Vipidia: EPAR—product information. 2022. [Online]. https://www.ema.europa.eu/en/documents/product-information/vipidia-epar-product-information_en.pdf

35. European Medicines Agency. Invokana: EPAR—product information. 2023. Accessed February 27, 2023. [Online]. https://www.ema.europa.eu/en/documents/product-information/invokana-epar-product-information_en.pdf

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.