The Adherence to Oral Second Line Antidiabetic Medication in People with Type 2 Diabetes

A Protocol for a Systematic Review

Nynne Sophie Holdt-Caspersen[1,2], Stine Hangaard Casper[2,3], Peter Vestergaard[3,4,5], Claus Dethlefsen[1,6], and Morten Hasselstrøm Jensen[2,3]

[1]Novo Nordisk, Biostatistics, Aalborg, Denmark
[2]Aalborg University, Health Science and Technology, Aalborg, Denmark
[3]Aalborg University Hospital, Steno Diabetes Center North Denmark, Aalborg, Denmark
[4]Aalborg University Hospital, Endocrinology, Aalborg, Denmark
[5]Aalborg University, Clinical Medicine, Aalborg, Denmark
[6]Aalborg University, Mathematical Sciences, Aalborg, Denmark

Abstract
The treatment goal in type 2 diabetes (T2D) is to keep the blood glucose within a target range. In the early stages of diabetes, the treatment may consist entirely of oral antidiabetics (OAD), which may be preferable over injectables for some people. However, previously published systematic reviews found a low OAD adherence and that the adherence differs between different OAD types. These systematic reviews were performed before 2015, and several new OADs have been marketed since then. Thus, a systematic review will be undertaken to review the newest studies on adherence to oral second line antidiabetics in people with T2D.

Keywords
Type 2 diabetes, Adherence, Oral antidiabetics, Systematic review, Protocol

1 INTRODUCTION

In 2021, an estimated total of 536.6 million people had diabetes [1], with approximately 90% of these cases being type 2 diabetes (T2D) [2]. Diabetes results in increased blood glucose, which leads to long-term complications [3]. Therefore, the treatment goal in diabetes is to keep the blood glucose within a target range to delay or avoid long-term complications [3]. The recommended initial treatment, referred to as first line treatment, for T2D is lifestyle interventions and treatment with metformin [3]. When the first line treatment fails to keep the blood glucose below the upper limit of the target range due to disease progression, additional antidiabetic medication, referred to as second line treatment, is added to the treatment regimen [3]. The recommended second line treatment for people with T2D and no comorbidities are glucagon-like peptide-1 receptor agonist (GLP-1RA), Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylurea, and thiazolidinedione (TZD) [3].

However, the general adherence to antidiabetic medication amongst people with T2D is low [4-6], which may result in suboptimal treatment effect and decreased glycaemic control. Several factors may affect the treatment adherence e.g., some patients may prefer oral medication over injectables. As several of the second line antidiabetic medication is available as OADs, the treatment regimen in the early stages of diabetes may consist entirely of OADs, which may be preferable for some patients. Iglay, et al. [5], Krass, et al. [6], and McGovern, et al. [7] all performed a systematic review and meta-analysis in which the adherence to different OAD drug classes were compared. These studies found that the adherence differed across the different OAD drug classes. The systematic reviews of Iglay, et al. [5], Krass, et al. [6], and McGovern, et al. [7] were performed prior to 2015, and several new OADs, such as oral semaglutide [8], have been marketed since then. Therefore, a systematic review including new literature will be undertaken with the aim to systematically review the adherence to oral second line antidiabetics in people with T2D.

2 METHODS

A systematic literature search will be performed to identify articles on adherence to oral second line antidiabetics in people with T2D. The search will be structured as a block search, which will consist of three independent blocks: 'T2D', 'Second line antidiabetics', and 'Adherence'. Each block will consist of relevant synonyms, both as free text and thesaurus term, if one exists. The search will be performed in the following databases: CINAHL, Cochrane, Embase, PsychInfo, PubMed, and Scopus.

The 18th Scandinavian Conference on Health informatics, Tromsø, Norway, August 22-24, 2022. Organized by UiT The Arctic University of Norway. Conference Proceedings published by Linköping University Electronic Press at https://doi.org/10.3384/ecp187.

Articles are included if they present original research on adherence to oral second line antidiabetics in people with T2D. The study population must be adults (≥18 years) with T2D and no other comorbidities living in developed countries. The study must be set during everyday circumstances i.e., not during Ramadan, the COVID-19 pandemic, or other special circumstances. Furthermore, the articles must be full text articles written in English. The selection process of relevant articles will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The quality of the included articles will be evaluated using Joanna Briggs Institute's (JBI's) critical appraisal tool.

Information extracted from the included articles will be details on the study design (control group, trial design, and trial duration), the participants (number of participants, demographics, and treatment regimen), adherence (adherence level and how adherence was measured), and potential adherence barriers.

The adherence level will be investigated with respect to the measurement method of adherence and the country of which the trial is set by dividing the extracted information into subsets.

3 RESULTS

The information extracted from the included articles will be presented in a systematic review. The reported level of adherence to oral second line antidiabetics will be presented in tables by subsets and summarised as a narrative synthesis.

4 DISCUSSION

The overview of adherence to different types of oral second line antidiabetic medication will be an addition to the previously obtained knowledge on the adherence to OADs in people with T2D. This updated overview will provide new knowledge on the patients' challenges to adhere to OADs, which may be used to investigate how these challenges might be overcome. A possible solution could be to use this knowledge to develop a decision support system to guide people with T2D on how to increase their adherence to OADs.

Furthermore, this review will provide an opportunity to compare the adherence rate of recently market OADs and OADs considered in the previously published systematic reviews.

The strength of the proposed systematic review is the broad scope of the search with no limitation on the study design, as this strategy ensures a relatively high recall of articles. The broad search may also be a limitation, as it may be difficult to compare adherence across studies with different study designs.

5 CONCLUSION

The systematic review will present an overview of the adherence to oral second line antidiabetic medications, including drugs marketed after 2015.

6 REFERENCES

[1] H. Sun *et al.*, "IDF diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045," *Diabetes research and clinical practice,* p. 109119, 2021.

[2] G. Xu *et al.*, "Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study," *Bmj,* vol. 362, 2018.

[3] M. J. Davies *et al.*, "Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)," *Diabetes Care,* vol. 41, no. 12, pp. 2669-2701, 2018, doi: 10.2337/dci18-0033.

[4] J. A. Cramer, "A systematic review of adherence with medications for diabetes," *Diabetes care,* vol. 27, no. 5, pp. 1218-1224, 2004.

[5] K. Iglay *et al.*, "Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral antihyperglycemic agents in type 2 diabetes," *Current medical research and opinion,* vol. 31, no. 7, pp. 1283-1296, 2015.

[6] I. Krass, P. Schieback, and T. Dhippayom, "Adherence to diabetes medication: a systematic review," *Diabetic Medicine,* vol. 32, no. 6, pp. 725-737, 2015.

[7] A. McGovern, Z. Tippu, W. Hinton, N. Munro, M. Whyte, and S. de Lusignan, "Comparison of medication adherence and persistence in type 2 diabetes: A systematic review and meta-analysis," *Diabetes, Obesity and Metabolism,* vol. 20, no. 4, pp. 1040-1043, 2018.

[8] U.S. Food and Drug Administration. "Rybelsus: Highlights of Prescribing Information." https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf (accessed 07-JAN-2022, 2022).

7 ACKNOWLEDGEMENT

This work was supported by a research grant from the Danish Diabetes Academy, which is funded by the Novo Nordisk Foundation, grant number NNF17SA00.