

CADTH Reference List

Metformin Extended Release Versus Immediate Release for Type 2 Diabetes

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Key Messages

- Two systematic reviews, 5 randomized controlled trials, and 2 non-randomized studies about the comparative clinical effectiveness of metformin extended release versus metformin immediate release for people with type 2 diabetes were identified.
- No economic evaluations were identified about the comparative cost-effectiveness of metformin extended release versus metformin immediate release for people with type 2 diabetes.

Research Questions

1. What is the comparative clinical effectiveness of metformin extended release versus metformin immediate release for people with type 2 diabetes?
2. What is the comparative cost-effectiveness of metformin extended release versus metformin immediate release for people with type 2 diabetes?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were extended release metformin and diabetes. The search was limited to English language documents published between January 1, 2017 and May 11, 2022. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in [Table 1](#). Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information available in the abstracts of selected publications.

Results

Two systematic reviews,^{1,2} 5 randomized controlled trials,³⁻⁷ and 2 non-randomized studies^{8,9} about the comparative clinical effectiveness of metformin extended release (ER) versus metformin immediate release (IR) for people with type 2 diabetes (T2D) were identified. No relevant economic evaluations about the comparative cost-effectiveness of metformin ER

Table 1: Selection Criteria

Criteria	Description
Population	People with type 2 diabetes
Intervention	Metformin extended release
Comparator	Metformin immediate release
Outcomes	Q1: Clinical effectiveness (e.g., hemoglobin A1C, mortality, quality of life, safety [e.g., adverse events]) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations

versus metformin IR for people with T2D were identified. Additionally, no health technology assessments were identified.

Additional references of potential interest that did not meet the inclusion criteria are provided in [Appendix 1](#).

Overall Summary of Findings

Two systematic reviews,^{1,2} 5 randomized controlled trials,³⁻⁷ and 2 non-randomized studies^{8,9} about the comparative clinical effectiveness of metformin ER versus metformin IR for people with T2D were identified. Guo et al. found that metformin sustained release resulted in a comparable effect on glycemic management and body weight in people with T2D taking metformin IR at 12 weeks.³ In the same study, a greater reduction in body weight, and incidence of overall and gastrointestinal (GI) adverse events was observed in individuals taking metformin ER compared to those taking metformin IR.³

One systematic review² and 3 randomized controlled trials^{4,5,7} found that metformin ER also had a similar effect on glycemic management when compared to the IR formulation of metformin. However, another systematic review found that metformin ER was associated with worse glycemic management compared to IR¹; whereas authors of a non-randomized study observed better glycemic management with metformin ER versus IR.⁶

In terms of adverse events, 1 systematic review² and 2 randomized controlled trials^{4,5} found no difference between metformin ER and IR. Another systematic review observed minimal improvement in dyspepsia but a similar incidence rate for other GI side effects with metformin ER compared to metformin IR.¹ Another non-randomized study observed a decrease in GI side effects in individuals with T2D that were switched from metformin IR to metformin ER.⁸

A randomized controlled trial found improvements in lipid profile and adipocytokines levels in individuals taking metformin ER compared to those taking metformin IR.⁶ The effect on body weight was similar between metformin ER and IR in a systematic review³ and a randomized controlled trial.⁶ Finally, improved adherence to medication was observed in people with metformin ER compared to metformin IR in a systematic review² and a non-randomized study.⁹ Although the language from identified studies was retained in certain cases for this

summary, it is recognized that terms such as adherence, compliance, and control may not account for factors that can impact the capacity of people living with T2D to cope with this condition. A detailed summary of the identified studies relevant to question 1 can be found in [Table 2](#).

No relevant economic evaluations were found about the comparative cost-effectiveness of metformin ER versus metformin IR for people with type 2 diabetes; therefore, no summary can be provided.

Table 2: Summary of Clinical Effectiveness Studies

Study citation	Study design, population	Intervention(s) and comparator	Relevant outcomes	Author's conclusions
Systematic reviews				
Abrilla et al. (2021) ¹	9 RCTs Population: adults with T2D N = 2,609	Intervention: Metformin ER Comparator: Metformin IR	A1C, GI symptoms (abdominal pain, diarrhea, dyspepsia, and nausea and vomiting)	Metformin ER was associated with statistically worse, but likely clinically similar A1C lowering and minimal improvement of GI intolerance compared to metformin IR.
Tan et al. (2021) ²	5 RCTs and 1 NRS Population: People with T2D N = 12,571	Intervention: Metformin ER Comparator: Metformin IR	A1C, fasting blood glucose, post-prandial glucose, abdominal pain, all cause death, any adverse events leading to treatment discontinuation, GI events	Metformin ER and IR formulations have similar effectiveness and safety. However, metformin ER was associated with improved compliance to treatment.
Randomized controlled trials				
Guo et al. (2021) ³	Study design: Randomized, open, and parallel controlled trial Population: People with T2D N = 886	Intervention: Metformin SR (Dulening) Comparator: Metformin IR	A1C, fasting blood glucose, weight loss, adverse drug reactions after 12 weeks of treatment	Metformin SR and metformin IR exhibited similar effects on A1C levels, fasting blood glucose and weight loss after 12 weeks of treatment. Metformin SR resulted in significantly lower overall adverse drug events and GI drug events compared to metformin IR.
Aggarwal et al. (2018) ⁴	Study design: Randomized, double-blinded trial Population: People with T2D N = 539	Intervention: Metformin ER Comparator: Metformin IR	A1C, fasting blood glucose, daily glucose after 24 weeks	Decrease in A1C and adverse events after 24 weeks of treatment was similar in individuals on metformin ER vs. IR.

Study citation	Study design, population	Intervention(s) and comparator	Relevant outcomes	Author's conclusions
Ji et al. (2018) ⁵⁷	Study design: open-label, multicenter, phase IV RCT Population: Treatment naïve Chinese individuals with T2D N = 532	Intervention: Metformin ER Comparator: Metformin IR	A1C, drug-related adverse events, GI adverse events at 16 weeks	Metformin ER was non-inferior to metformin IR for change in A1C at 16 weeks. Metformin ER resulted in similar incidences of overall adverse events and GI adverse events compared to metformin IR.
Derosa et al. (2017) ⁶	Study design: RCT Population: Caucasian individuals with T2D N = 253	Intervention: Metformin ER Comparator: Metformin IR	A1C, body weight, postprandial glucose, fasting plasma insulin, homeostasis model assessment in insulin resistance, levels of adipocytokines, and patient satisfaction at 6 months	Metformin ER and metformin IR resulted in similar decrease of body weight and BMI. Metformin ER resulted in greater improvement in glycemic control, fasting plasma insulin resistance, lipid profile, and levels of some adipocytokines.
Hameed et al. (2017) ⁷	Study design: RCT Population: People with T2D N = 90	Intervention: Metformin ER Comparator: Metformin IR	A1C, fasting blood glucose, and random blood sugars at 3 months	Metformin ER and IR resulted in similar reduction in fasting and random blood sugar at 3 months.
Non-randomized studies				
Mazumder et al. (2017) ⁸	Study design: Prospective cohort Population: Adults with T2D N = 702	Intervention: Metformin ER and SR Comparator: Metformin IR	A1C, GI side effects	Adults who switched to metformin SR and ER from metformin IR experienced reduced GI side effects with no further side effects.
Hostalek et al. (2017) ⁹	Study design: Prospective cohort Population: People with T2D N = 201	Intervention: Metformin ER and SR Comparator: Metformin IR	Adherence to therapy, patient preference	Adherence to Metformin ER was good to excellent, and there was a strong preference for metformin ER over metformin IR.

BMI = body mass index; A1C = hemoglobin A1C; GI = gastrointestinal; IR = immediate release; NR = not reported; NRS = non-randomized study; RCT = randomized controlled trial; SR = sustained release; T2D = type 2 diabetes; ER = extended release.

References

Health Technology Assessments

No literature identified.

Systematic Reviews

1. Abrilla AA, Pajes A, Jimeno CA. Metformin extended-release versus metformin immediate-release for adults with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract.* Aug 2021; 178: 108824. [PubMed](#)
2. Tan J, Wang Y, Liu S, et al. Long-Acting Metformin Vs. Metformin immediate release in patients with type 2 diabetes: a systematic review. *Front Pharmacol.* 2021; 12: 669814. [PubMed](#)

Randomized Controlled Trials

3. Guo LX, Liu GE, Chen L, et al. Comparison of clinical efficacy and safety of metformin sustained-release tablet (II) (Dulening) and metformin tablet (Glucophage) in treatment of type 2 diabetes mellitus. *Front Endocrinol (Lausanne).* 2021; 12: 712200. [PubMed](#)
4. Aggarwal N, Singla A, Mathieu C, et al. Metformin extended-release versus immediate-release: an international, randomized, double-blind, head-to-head trial in pharmacotherapy-naive patients with type 2 diabetes. *Diabetes Obes Metab.* 2018; 20(2): 463-467. [PubMed](#)
5. Ji L, Liu J, Yang J, et al. Comparative effectiveness of metformin monotherapy in extended release and immediate release formulations for the treatment of type 2 diabetes in treatment-naive Chinese patients: analysis of results from the CONSENT trial. *Diabetes Obes Metab.* 2018; 20(4): 1006-1013. [PubMed](#)
6. Derosa G, D'Angelo A, Romano D, Maffioli P. Effects of metformin extended release compared to immediate release formula on glycemic control and glycemic variability in patients with type 2 diabetes. *Drug Des Devel Ther.* 2017; 11: 1481-1488. [PubMed](#)
7. Hameed M, Khan K, Salman S, Mehmood N. Dose comparison and side effect profile of metformin extended release versus metformin immediate release. *J Ayub Med Coll Abbottabad.* Apr-Jun 2017; 29(2): 225-229. [PubMed](#)

Non-Randomized Studies

8. Mazumder A, Singh A, Jha S. Study of side effects of metformin immediate release in comparison with sustained and extended release in type 2 diabetic patients of a tertiary care hospital in North India. *Int J Pharm Res.* 2021; 13(2): 1934-1939.
9. Hostalek U, Ametov A, Barykina I, Bondar I, Vaysberg A, et al. Multicentre evaluation of adherence to extended-release metformin in daily practice in Russia. *Int J Diabetes Clin Res.* 2017; 4:078. [10.23937/2377-3634/1410078](https://doi.org/10.23937/2377-3634/1410078).

Appendix 1: References of Potential Interest

Systematic Reviews

Unclear Population – Not Specific to People with T2D

10. Tarry-Adkins JL, Grant ID, Ozanne SE, Reynolds RM, Aiken CE. Efficacy and side effect profile of different formulations of metformin: a systematic review and meta-analysis. *Diabetes Ther.* Jul 2021; 12(7): 1901-1914. [PubMed](#)

Protocols

11. Feliciano-Alfonso JE, Nivia Fonseca DA, Oliveros-Rodríguez H. Safety profile of prolonged/extended-release metformin vs. immediate-release metformin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. (CRD42021244246). *PROSPERO: International prospective register of systematic reviews.* York (GB): University of York Centre for Reviews and Dissemination; 2021. https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42021244246 Accessed 2022 May 16.
12. Mao P, Tsai M, Chung M, Hsu L. Comparison of efficacy and safety of metformin extended release relative to metformin immediate release in type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. (CRD42020190947). *PROSPERO: International prospective register of systematic reviews.* York (GB): University of York Centre for Reviews and Dissemination; 2020. https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42020190947 Accessed 2022 May 16.
13. Li H, Sun H. Efficacy and safety of extended-release metformin vs. immediate-release metformin in patients with type 2 diabetes: a systematic review and meta-analysis. (CRD42017055487). *PROSPERO: International prospective register of systematic reviews.* York (GB): University of York Centre for Reviews and Dissemination; 2017. https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42017055487 Accessed 2022 May 16.

Randomized Controlled Trials

Alternative Intervention

14. Henry RR, Frias JP, Walsh B, et al. Improved glycemic control with minimal systemic metformin exposure: effects of Metformin Delayed-Release (Metformin DR) targeting the lower bowel over 16 weeks in a randomized trial in subjects with type 2 diabetes. *PLoS One.* 2018; 13(9): e0203946. [PubMed](#)
15. Kim JD, Park CY, Cha BY, et al. Comparison of adherence to glimepiride/metformin sustained release once-daily versus glimepiride/metformin immediate release BID fixed-combination therapy using the medication event monitoring system in patients with type 2 diabetes. *Clin Ther.* 05 2018; 40(5): 752-761.e2. [PubMed](#)

Protocol

16. Merck KGaA, Darmstadt, Germany. NCT02252965. Metformin extended release versus metformin immediate release in subjects with type 2 diabetes (CONSENT). *ClinicalTrials.gov.* Bethesda (MD): U.S. National Library of Medicine; 2017. <https://clinicaltrials.gov/ct2/show/NCT02252965A> Accessed 2022 May 16.

Non-Randomized Studies – Alternative Comparator

17. Meyers AG, Hudson J, Cravalho CKL, et al. Metformin treatment and gastrointestinal symptoms in youth: Findings from a large tertiary care referral center. *Pediatr Diabetes.* 03 2021; 22(2): 182-191. [PubMed](#)

Economic Evaluations

Budget Impact Analysis

18. Gout-Zwart JJ, de Jong LA, Saptanno L, Postma MJ. Budget impact analysis of metformin sustained release for the treatment of type 2 diabetes in the Netherlands. *Pharmacoeconom Open.* Jun 2020; 4(2): 321-330. [PubMed](#)

Conference Poster

19. Alsultan M, Al-Omar H, Vandewalle B, Placido M, Afonso-Silva M, Mota M, et al. Metformin extended versus immediate release in Saudi Arabia: a cost-effectiveness analysis. (ISPOR 20th Annual European Congress, Research Poster Presentations). *Value in Health.* 2017;20(9):PA479. [https://www.valueinhealthjournal.com/article/S1098-3015\(17\)30790-8/fulltext](https://www.valueinhealthjournal.com/article/S1098-3015(17)30790-8/fulltext) Accessed 2022 May 16.

Reviews

20. Bonnet F, Scheen A. Understanding and overcoming metformin gastrointestinal intolerance. *Diabetes Obes Metab.* 04 2017; 19(4): 473-481. [PubMed](#)