CoLab Network

Appraisal of Observational Evidence

Exploration of the Risk of Suicidality and Self-Harm With Glucagon-Like Peptide-1 Receptor Agonists

Authors: Samy Suissa, Samantha Shapiro, Laurent Azoulay, Melissa Severn, Audray St-Jean, Carolina Moriello

This appraisal was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) through the Post-Market Drug Evaluation CoLab Network.

May 2024

Key Messages

Safety concerns about the use of glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have recently been raised, including a potential increased risk of self-harm and suicidal ideation.

We conducted a critical appraisal of the available real-world evidence to evaluate the association between GLP-1 RAs and the risk of suicidality and self-harm among patients with type 2 diabetes or obesity.

To date, only 2 observational studies have been published assessing this potential association.

The potential association between GLP-1 RAs and suicidality is limited, as the studies had contradictory evidence and methodological limitations. Conducting a large observational study that can mitigate time-related biases and provide robust evidence on the potential association between GLP-1 RAs and suicidality may address the methodological challenges.

Table of Contents

List of Tables

Abbreviations

CI	confidence interval
GLP-1	glucagon-like peptide-1
HR	hazard ratio
OR	odds ratio
RA	receptor agonist

Introduction and Rationale

Background

Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are a relatively newer class of antidiabetic drugs used to treat type 2 diabetes.[1] In addition to their glycemic management properties, they also contribute to appetite suppression and weight loss. Table 1 lists the GLP-1 RAs currently or previously available in Canada for glycemic control. Some products (semaglutide and liraglutide) also have an indication for weight management. However, there are other GLP-1 RAs being used off-label for weight loss.[2-4]

Recently, reports of suicidal thoughts and self-harm behaviours have been reported in individuals using liraglutide and semaglutide drugs. This has led to concerns regarding potential associations between GLP-1 RAs and the risk of self-harm behaviour and suicidal ideation (thoughts of suicide).[5] There are multiple hypothesized mechanisms for a potential association between GLP-1 RA use and depression and suicidality, such as hyperactivity of the hypothalamic-pituitary-adrenal axis,[6] the mental impact of sudden weight loss,[7,8] brain-derived neurotrophic factor dysregulation,[9,10] and modulation of neuroinflammation.[11] Complex relationships exist between overweight or obesity, weight loss, and depression and suicide. Indeed, higher rates of depression, self-harm behaviours, and suicide have been observed among patients who have undergone bariatric surgery,[12-14] highlighting the potential impact of weight loss on adverse psychiatric outcomes. GLP-1 RAs can additionally cross the blood-brain barrier[15] and exert effects on the brain.[16] Currently, there is no clear consensus on whether there is a biological relationship between GLP-1 RAs and depression or suicidality, and if so, what that mechanism is.

Health Canada has launched a signal assessment to investigate the risk of suicide, self-harm behaviour, suicidal ideation, and self-injurious ideation (thoughts of self-harm) with the use of GLP-1 RAs. This critical appraisal evaluated the existing observational studies available in the literature to provide a better understanding of the quality of the methodologies used to identify this safety concern.

Table 1: GLP-1 Receptor Agonists Marketed in Canada

Drug	Brand name	Indication	Manufacturer
Semaglutide	Ozempic	Type 2 diabetes	Novo Nordisk Canada Inc.
	Rybelsus	Type 2 diabetes	
	Wegovy	Weight management	
Liraglutide	Victoza	Type 2 diabetes	
	Saxenda	Weight management	
Liraglutide combined with insulin degludec	Xultophy	Type 2 diabetes	
Dulaglutide	Trulicity	Type 2 diabetes	Eli Lilly Canada Inc.
Lixisenatide	Adlyxine[a]	Type 2 diabetes	sanofi-aventis Canada Inc.
Lixisenatide combined with insulin glargine	Soliqua	Type 2 diabetes	

Drug	Brand name	Indication	Manufacturer
Exenatide[b]	Byetta	Type 2 diabetes	AstraZeneca Canada Inc.
	Bydureon	Type 2 diabetes	

GLP-1 = glucagon-like peptide-1.

[a]Adlyxine (lixisenatide) is no longer available in Canada (discontinued November 2023).

[b]Bydureon and Byetta (exenatide) are no longer available in Canada (discontinued September 2022).

Policy Issue

The use of GLP-1 RAs is increasing. Health Canada is conducting a signal assessment investigating the risk of suicide, self-harm, suicidal ideation (thoughts of suicide), and self-injurious ideation (thoughts of self-harm) with the use of GLP-1 RAs. The scope of their signal assessment includes reviews of the literature, pharmacovigilance databases, and other local and international information. Their objective is to determine if regulatory actions are warranted for the GPL-1 RAs used in type 2 diabetes. With this query, Health Canada wishes to obtain real-world safety evidence to incorporate into their signal assessment.

Policy Questions

1. Are GLP-1 RAs associated with suicidality and/or self-harm behaviours?
2. Are GLP-1 RAs associated with suicidality and/or self-harm behaviour in patient subgroups (Sex- and Gender-Based Analysis Plus, as mandated by the Government of Canada)?
3. Are GLP-1 RAs associated with other mental health disorders relevant to suicidality and self-harm behaviours identified by a panel of mental health experts?

Main Take-Away

GLP-1 RAs are antidiabetic drugs used to treat type 2 diabetes. Recently, there have been reports of suicide and self-harm in patients treated with these drugs. This study aims to evaluate and critically appraise the existing evidence in published real-world studies.

Purpose

Prior to conducting a de novo observational study, we need to determine if the policy questions can be answered using existing publications. As such, an evidence review with a critical appraisal will be undertaken to evaluate and critically appraise the published real-world studies, to provide guidance as to which findings are credible and transferable to decision-making, and to identify gaps in the evidence.

Research Question

This study aims to review and critically appraise the existing evidence in published real-world studies regarding the risk of suicidality and/or self-harm behaviour with the use of GLP-1 RAs among patients with type 2 diabetes or patients with obesity who do not have diabetes.

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, and the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevance. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were glucagon-like peptide-1, incretin mimetics, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, and mental health. CADTH-developed search filters were applied to limit retrieval to observational studies or real-world evidence using routinely collected data. Neither case reports nor case series were included in the search results. No date limit was applied, but the search was limited to English-language documents. The search was completed on February 22, 2024. A clinical trial registry (clinicaltrials.gov) was searched on February 26, 2024, on the drugs under review for the specified indication, limited to all observational studies. Database and trial registry search alerts were completed on March 29, 2024.

A supplemental literature search was completed on February 29, 2024, using MEDLINE and Embase. The main search concepts were glucagon-like peptide-1, incretin mimetics, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, and mental health. CADTH-developed search filters were applied to limit retrieval to randomized controlled trials, controlled clinical trials, or any other type of clinical trial. No date limit was applied, but the search was limited to English-language documents.

The literature search strategy is included in Appendix 1.

Warning: Appendix 1 includes antiquated, noninclusive, and potentially stigmatizing and harmful mental health terms. The authors of this review recognize and acknowledge the inappropriate and harmful nature of these terms and will indicate where they are written so that the reader can determine how they would like to proceed.

Selection Criteria and Methods

Two reviewers screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was determined by 1 reviewer based on the inclusion criteria presented in Table 2.

In addition, 1 reviewer screened citations for randomized controlled trials and controlled clinical trials. This was done to identify the existing literature for the purpose of context and the citations were not critically appraised.

Table 2: Selection Criteria for Observational Studies Examining the Risk of Suicidality and Self-Harm

Criteria	Description
Population	Patients with type 2 diabetes or patients with obesity
Interventions	Semaglutide Liraglutide Liraglutide combined with insulin degludec Dulaglutide Lixisenatide Lixisenatide combined with insulin glargine Exenatide
Comparator	Any comparator
Outcomes	Suicide Self-harm Suicidal ideation (thoughts of suicide) Self-injurious ideation (thoughts of self-harm) Other mental health outcomes related to suicide that may emerge during the literature search screening
Study design	Comparative observational studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 2 or were duplicate publications.

Appraisal Approach

The methods sections of the included studies were reviewed for various sources of bias, including important biases specific to the pharmacoepidemiologic literature such as prevalent user bias and time-related biases.[17-19] The available information on study design, exposure and outcome definitions, and statistical analysis was assessed.

Summary of Evidence

Main Take-Away

Two comparative observational studies reporting on the risk of suicidality or self-harm met the inclusion criteria. The first study used a primary care database from the UK and included 16,190 patients. The second study used electronic health records from patients across the US and included 105,566 patients with overweight or obesity and 55,542 patients with type 2 diabetes. The studies had contradictory evidence on the association between GLP-1 RA use and the risk of suicidality or self-harm, and both had limitations in the methods used.

Quantity of Research Available

A total of 492 citations were identified in the literature search. Following screening of titles and abstracts, 485 citations were excluded and 7 potentially relevant reports from the electronic search were retrieved for full-text review. Of these, 2 comparative observational studies reporting on suicidality and self-harm met the inclusion criteria and were appraised in this report. An additional 2 publications on other mental health outcomes were summarized descriptively. No citations were retrieved from the grey literature. The evidence from randomized controlled trials and pharmacovigilance analyses is summarized for completeness, and to provide context on the subject, in Appendix 2 and Appendix 3. Other publications of interest are listed in Appendix 4 (1 randomized controlled trial) and Appendix 5 (4 noncomparative observational studies).

Study Characteristics and Findings

Comparative Observational Studies Assessing Suicidality and Self-Harm

Characteristics and findings of the 2 included observational studies examining the risk of suicidality and self-harm are reported in Table 3. Both were retrospective cohort studies, with 1 using data from the UK and the other from the US..[20,21]

The study by Gamble et al. (2018)[20] used the Clinical Practice Research Datalink (CPRD), a primary care database from the UK that is largely representative of the UK population. The study included 16,910 patients newly exposed to GLP-1 RAs or sulfonylureas and followed for a mean duration ranging from 292 days to 397 days. Patients were excluded if they had a history of depression, self-harm, anxiety, or other serious psychiatric conditions in the year before receiving the respective treatments. The primary study outcome was a composite of either new-onset depression or self-harm, including suicide and suicidal ideation. After using a high-dimensional propensity score algorithm and adjusting on deciles of the propensity score and on the number of glucose-lowering agents used during follow-up, the authors did not find a statistically significant association between GLP-1 RA use and the composite outcome when comparing patients using a GLP-1 RA to those using a sulfonylurea (hazard ratio [HR]: 1.25; 95% confidence interval [CI], 0.63 to 2.50).

The second study by Wang et al. (2024)[21] used the TriNetX Analytics platform, which contains electronic health records from patients across the US. The study included 2 cohorts, 1 with105,566 patients with overweight or obesity who were prescribed either semaglutide (Wegovy, which is a GLP-1 RA) or a non–GLP-1 RA anti-obesity medication, and 1 with 55,542 patients with type 2 diabetes who were prescribed either

semaglutide (Ozempic) or a non–GLP-1 RA antidiabetes medication. In the overweight or obesity cohort, the mean duration of follow-up was 160.5 days for those treated with semaglutide (Wegovy) and 150.2 days for those treated with a nonGLP-1 RA anti-obesity medication. In the type 2 diabetes cohort, the mean duration of follow-up ranged from 167.2 to 172.9 days. The study outcome was suicidal ideation in the first 6 months following cohort entry for both groups. Additional outcomes included suicide attempt among patients with overweight and obesity; and suicidal ideation in the first year, 2 years, and 3 years following cohort entry among patients with type 2 diabetes. Patients in both exposure groups in each cohort were matched on propensity score. In patients with overweight and obesity without a history of suicidal ideation, patients with overweight and obesity with a history of suicidal ideation, patients with type 2 diabetes without a history of suicidal ideation, and patients with type 2 diabetes with a history of suicidal ideation, the HRs for suicidal ideation were 0.27 (95% CI, 0.20 to 0.36), 0.44 (0.32 to 0.60), 0.36 (0.25 to 0.53), and 0.51 (0.31 to 0.83), respectively.

Comparative Observational Studies Assessing all Other Mental Health Outcomes

Table 4 summarizes the characteristics and findings of the remaining 2 studies examining the risk of all other mental health outcomes. The study by Tsai et al. (2022)[22] was a retrospective cohort study including 53,456 patients with diabetes in Taiwan. The HR for the composite outcome of incident depression and/or anxiety was 0.80 (95% CI, 0.67 to 0.95) when comparing use of GLP-1 RAs with non-use. The mean duration of follow-up was 2.6 years for GLP-1 RA users and 2.0 years for non-users.

The second study by Wium-Andersen et al. (2022)[23] was a nested case-control study including 73,869 patients with incident type 2 diabetes in Denmark. The primary outcome was a composite of depression or the start of antidepressant medication. Over a mean follow-up of 10 years in cases and 11 years in controls, the odds ratio (OR) for the association between GLP-1 RAs and depression was 0.88 (95% CI, 0.80 to 0.97) for users of GLP-1 RAs compared with non-users.

Appraisal of Evidence

To date, only 2 observational studies have been conducted to assess the potential association between GLP-1 RAs and the risk of suicidality or self-harm. The main limitations of the methodologies applied are described subsequently. The observational studies of GLP-1 RAs and other mental health outcomes are not critically appraised in this report.

Gamble et al. (2018)

Patients with a history of depression, self-harm, anxiety, and other serious psychiatric conditions in the year before cohort entry were excluded from the study by Gamble et al. (2018). However, these patients may represent those who are at the highest risk of the outcome and most susceptible to an exposure trigger; therefore, the effects of GLP-1 RAs in these patients would be highly relevant. Furthermore, as only 501 GLP-1 RA users were identified in the study and the outcome was relatively rare, the authors were not able to assess self-harm as a separate outcome due to the small number of events. Due to the small sample size and rarity of the outcome, the results were also imprecise, with wide CIs for the HR (0.63 to 2.50).

Table 3: Characteristics and Findings of the Included Observational Studies Examining the Risk of Suicidality and Self-Harm

First author (year)	Data source	Study design	Sample size[a]	Exposure	Outcome	Adjusted hazard ratio (95% CI)	Duration of follow-up[a]
Gamble et al. (2018)[20]	UK Clinical Practice Research Datalink (January 2007-February 2016)	Cohort	16,910	GLP-1 RAs vs. sulfonylureas	Composite of new-onset depression or self-harm (including suicide and suicidal ideation)	Composite: 1.25 (0.63 to 2.50) Depression: 0.98 (0.36 to 2.61) Self-harm: NR	GLP-1 RAs: 397 days Sulfonylureas: 292 days
Wang et al. (2024)[21]	US TriNetX Analytics Network (June 2021 to December 2022)	Cohort	Overweight or obesity: 105,566	Semaglutide (Wegovy) vs. non–GLP-1 RA anti-obesity medications[b]	First or recurrent suicidal ideation	Incident: 0.27 (0.20 to 0.36) Recurrent: 0.44 (0.32 to 0.60)	Semaglutide (Wegovy) 160.5 days Comparator: 150.2 days
Wang et al. (2024)[21]	US TriNetX Analytics Network (December 2017 to May 2021)	Cohort	Type 2 diabetes: 55,452	Semaglutide (Ozempic) vs. non–GLP-1 RA antidiabetes medications[c]	First or recurrent suicidal ideation	Incident: 0.36 (0.25 to 0.53) Recurrent: 0.51 (0.31 to 0.83)	Semaglutide (Ozempic) 172.9 days Comparator: 167.2 days

CI = confidence interval; GLP-1 = glucagon-like peptide-1; ICD-10 = International Classification of Diseases, 10th revision; NR = not reported; RA = receptor agonist; vs. = versus.

Note: Data for Wang et al. (2024) are presented for patients with overweight or obesity and patients with type 2 diabetes, separately.

[a]Study population and mean duration of follow-up for primary outcome.

[b]Non–GLP-1 RA anti-obesity medications include bupropion, naltrexone, orlistat, topiramate, phentermine, and setmelanotide.

[c]Non–GLP-1 RA antidiabetes medications include insulin, metformin, sulfonylureas, alpha glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors.

Table 4: Characteristics of the Included Observational Studies Examining the Risk of Other Mental Health Outcomes

First author (year)	Data source	Study design	Sample size[a]	Exposure	Outcome	Adjusted HR or OR (95% CI)[a]	Duration of follow-up[a]
Tsai et al. (2022)[22]	Taiwan National Health Insurance Research Database (2011 to 2017)	Cohort	Diabetes: 53,456	GLP-1 RAs[b] vs. non-use	Composite of incident depression and/or anxiety	Adjusted HR Composite: 0.80 (0.67 to 0.95) Anxiety: 0.78 (0.64 to 0.95) Depression: 0.94 (0.72 to 1.23)	GLP-1 RAs: 2.6 years Non-users: 2.0 years
Wium-Andersen et al. (2022)[23]	Denmark National Registries (2000 to 2012)	Nested case-control	Incident type 2 diabetes: 73,869	GLP-1 RAs[c] vs. non-use	Depression or start of antidepressant medication	Adjusted OR 0.88 (0.80 to 0.97)	Cases: 10 years Controls: 11 years

CI = confidence interval; GLP-1 = glucagon-like peptide-1; HR = hazard ratio; OR = odds ratio; RA = receptor agonist; vs. = versus.

Note: Data for Wium-Andersen et al. (2022) are presented from a subgroup of overall cases and controls.

[a]Study population and mean duration of follow-up for primary outcome.

[b]GLP-1 RAs include liraglutide, dulaglutide, and exenatide.

[c]GLP-1 RAs include exenatide, liraglutide, lixisenatide, semaglutide, and dulaglutide.

The exposure definition and censoring criteria in the study by Wang et al. (2024) were unclear. It was not reported whether a patient who initiated a comparator medication but switched to semaglutide would be classified as a semaglutide user or a comparator user. In addition, if they were classified as a comparator user, it was unclear whether they would be censored upon switching to semaglutide. It is also unclear if suicidal ideation events were attributed to the correct exposure groups. Finally, the classification of exposed person-time could have led to immortal time bias, a bias that results in underestimating the effect of a drug and can thus make elevated risks appear falsely beneficial. It is also unclear whether prevalent comparator drug users were included in the study, which may have led to bias from depletion of susceptibles and selection bias from including prevalent users. Because the latency of the potential exposure-outcome relationship is unknown, it is unclear in which direction this may have biased the observed association. The choice of comparator medications also may have led to selection bias and confounding by indication, especially for the cohort of patients with overweight and obesity. Indeed, many of the comparator drugs used in the overweight and obesity cohort have been associated with increased risks of depression and suicidal ideation (e.g., topiramate, phentermine, setmelanotide) or are prescribed for conditions associated with depression and suicidal ideation (e.g., bupropion, naltrexone). Such confounding by unmeasured indication resulting from the choice of comparator medications would likely make GLP-1 RA use appear protective in comparison. Furthermore, the HR for the analysis of suicide attempt was not reported and self-harm was not assessed as an end point.

Table 5: Potential Sources of Bias of Included Observational Studies Examining the Risk of Suicidality and Self-Harm

First author (year)	Confounding by indication	Immortal time bias	Selection bias	Outcome misclassification[a]	Other limitations
Gamble et al. (2018)[20]	No	No	No	Yes	Small sample size
Wang et al. (2024)[21]	Yes	Yes	Yes	Yes	Inappropriate comparator

[a]For both studies, there was a short duration of follow-up time for the outcome.

Conclusions and Next Steps

Main Take-Away

The current available literature has limited evidence to demonstrate whether there is a link between the use of GLP-1 RAs and risk of suicidality and self-harm. This is mainly due to limitations in the methods used in the studies. A large, well-designed observational study is necessary to determine this potential association.

In summary, the scientific literature of observational studies regarding the potential link between GLP-1 RAs and suicidality is both limited and contradictory. Additionally, the few studies using real-world data are limited by significant methodological limitations, including small sample sizes and biases related to time.

These methodological challenges could be addressed through the implementation of large observational studies specifically designed to mitigate time-related biases and provide robust evidence concerning the potential association between GLP-1 RAs and suicidality.

Note: The literature regarding GLP-1 RAs and other mental health outcomes are only described in this report, and any conclusions regarding the quality of evidence and methodologies would require a critical appraisal of this literature.

References

1. Glucagon-like peptide-1 (GLP-1) receptor agonists: risk of aspiration during anesthesia. Ottawa (ON): Institute for Safe Medication Practices Canada; 2023: https://ismpcanada.ca/wp-content/uploads/ISMPCSB2023-i9-GLP-1.pdf. Accessed 2024 Apr 23.
2. Public Health Agency of Canada. Snapshot of Diabetes in Canada. 2024: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/snapshot-diabetes-canada-2023.html. Accessed 2024 Apr 23.
3. Vannabouathong C CC, Le K, Eurich D, Dyrda P. Current utilization patterns of glucagon-like peptide-1 receptor agonists. *Can J Health Technol.* 2022;2(9). https://canjhealthtechnol.ca/index.php/cjht/article/view/HC0042. Accessed 2024 Apr 23.
4. Diabetes Canada Clinical Practice Guidelines Expert Committee, Lipscombe L, Butalia S, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update. *Can J Diabetes*. 2020;44(7):575-591. PubMed
5. European Medicines Agency. EMA statement on ongoing review of GLP-1 receptor agonists. 2023: https://www.ema.europa.eu/en/news/ema-statement-ongoing-review-glp-1-receptor-agonists. Accessed 2024 Apr 23.
6. Ruggiero R, Mascolo A, Spezzaferri A, et al. Glucagon-like Peptide-1 Receptor Agonists and Suicidal Ideation: Analysis of Real-Word Data Collected in the European Pharmacovigilance Database. *Pharmaceuticals (Basel)*. 2024;17(2). PubMed
7. Hecht LM, Yeh HH, Braciszewski JM, et al. Weighing the Association Between BMI Change and Suicide Mortality. *Psychiatr Serv*. 2021;72(8):920-925. PubMed
8. Elovainio M, Shipley MJ, Ferrie JE, et al. Obesity, unexplained weight loss and suicide: the original Whitehall study. *J Affect Disord*. 2009;116(3):218-21. PubMed
9. Xie X, Yang H, An JJ, et al. Activation of Anxiogenic Circuits Instigates Resistance to Diet-Induced Obesity via Increased Energy Expenditure. *Cell Metab*. 2019;29(4):917-931 e4. PubMed
10. Nepon J, Belik SL, Bolton J, Sareen J. The relationship between anxiety disorders and suicide attempts: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Depress Anxiety*. 2010;27(9):791-8. PubMed
11. Kim Y-K KO, Song J. Alleviation of Depression by Glucagon-Like Peptide 1 Through the Regulation of Neuroinflammation, Neurotransmitters, Neurogenesis, and Synaptic Function. Front Pharmacol. 2020;200;11(1270).
12. Castaneda D, Popov VB, Wander P, Thompson CC. Risk of Suicide and Self-harm Is Increased After Bariatric Surgery-a Systematic Review and Meta-analysis. *Obes Surg*. 2019;29(1):322-333. PubMed
13. Smith VA, Maciejewski ML, Berkowitz TSZ, et al. The Effect of Bariatric Surgery on Long-term Depression Treatment in Patients With Obesity. *Ann Surg*. 2022;276(2):318-323. PubMed
14. Muller A, Hase C, Pommnitz M, de Zwaan M. Depression and Suicide After Bariatric Surgery. *Curr Psychiatry Rep*. 2019;21(9):84. PubMed
15. Fu Z, Gong L, Liu J, et al. Brain Endothelial Cells Regulate Glucagon-Like Peptide 1 Entry Into the Brain via a Receptor-Mediated Process. *Front Physiol*. 2020;11:555. PubMed
16. Baggio LL, Drucker DJ. Glucagon-like peptide-1 receptors in the brain: controlling food intake and body weight. *J Clin Invest*. 2014;124(10):4223-6. PubMed
17. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-20. PubMed
18. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. *Diabetes Care*. 2012;35(12):2665-73. PubMed
19. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 2020;29(9):1101-1110. PubMed
20. Gamble JM, Chibrikov E, Midodzi WK, Twells LK, Majumdar SR. Examining the risk of depression or self-harm associated with incretin-based therapies used to manage hyperglycaemia in patients with type 2 diabetes: a cohort study using the UK Clinical Practice Research Datalink. *BMJ Open*. 2018;8(10):e023830. PubMed

21. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nat Med*. 2024;30(1):168-176. PubMed

22. Tsai WH, Sung FC, Chiu LT, Shih YH, Tsai MC, Wu SI. Decreased Risk of Anxiety in Diabetic Patients Receiving Glucagon-like Peptide-1 Receptor Agonist: A Nationwide, Population-Based Cohort Study. *Front Pharmacol*. 2022;13:765446. PubMed

23. Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Diabetes, antidiabetic medications and risk of depression - A population-based cohort and nested case-control study. *Psychoneuroendocrinology*. 2022;140:105715. PubMed

24. Silverii GA, Marinelli C, Mannucci E, Rotella F. Glucagon-like peptide-1 receptor agonists and mental health: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2024. [online ahead of print] PubMed

25. Chen C, Zhou R, Fu F, Xiao J. Postmarket safety profile of suicide/self-injury for GLP-1 receptor agonist: a real-world pharmacovigilance analysis. *Eur Psychiatry*. 2023;66(1):e99. PubMed

26. Zhou J, Zheng Y, Xu B, et al. Exploration of the potential association between GLP-1 receptor agonists and suicidal or self-injurious behaviors: a pharmacovigilance study based on the FDA Adverse Event Reporting System database. *BMC Med*. 2024;22(1):65. PubMed

27. McIntyre RS, Mansur RB, Rosenblat JD, Kwan ATH. The association between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: reports to the Food and Drug Administration Adverse Event Reporting System (FAERS). *Expert Opin Drug Saf*. 2024;23(1):47-55. PubMed

28. Whitmore C. Type 2 diabetes and obesity in adults. *Br J Nurs*. 2010;19(14):880, 882-6. PubMed

29. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220-9. PubMed

30. Semenkovich K, Brown ME, Svrakic DM, Lustman PJ. Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. *Drugs*. 2015;75(6):577-87. PubMed

Authors and Contributors

Authors

CNODES disclaimer: The opinions and conclusions contained in this report are those of the authors. No endorsement by CADTH or Health Canada is intended or should be inferred.

Clinical Review

Samy Suissa reviewed and critically appraised the articles related to this project, and reviewed and approved the final draft of the report.

Samantha Shapiro reviewed and critically appraised the articles related to this project, and reviewed and approved the final draft of the report.

Laurent Azoulay reviewed and critically appraised the articles related to this project, and reviewed and approved the final draft of the report.

Melissa Severn contributed the literature search methods, designed the search strategy, and reviewed and approved the final draft of the report.

Audray St-Jean drafted and reviewed the report.

Carolina Moriello drafted and reviewed the report.

Contributors

CNODES is a collaborating core network partner for CoLab, which is funded for query-related activity by CADTH (grant number C222 360). The CNODES team is led by the CNODES steering committee and comprises many researchers who have provided significant support to this project.

CADTH would like to acknowledge the following individuals:

Christine Perras and Karleen Girn conducted the first-level screening. Danielle MacDougall executed the literature search strategy and prepared results for screening. David Kaunelis peer reviewed the search strategy. Hannah Loshak prepared the references for publication. Christine Perras and David Stock reviewed the drafts and final report. Emily Farrell provided knowledge mobilization support. Brandy Appleby provided project management support.

Conflicts of Interest

Samy Suissa disclosed the following:

Speaking engagements:

Boehringer-Ingelheim (2020 to 2022): COPD research

Covispharma (2023): COPD research

Payment as advisor or consultant:

AtaraBio (2019 to 2023): Tab-cel

Boehringer-Ingelheim (2018 to 2022): COPD research

Harvard Brigham and Women's Hospital (2018 to 2022): RCT-DUPLICATE and eMRISE projects

Harvard Pilgrim Health Care Institute (2021 to 2023): FDA Sentinel project

Novartis (2018 to 2022): Asthma trials

Laurent Azoulay disclosed the following:

Pfizer: Advisory committee (2023 to present)

Speaking engagements:

Roche (2022): Lecture

Payment as advisor or consultant:

Pfizer: Lecture

No other conflicts of interest were declared.

Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Warning: There are many cases where antiquated, noninclusive, and potentially stigmatizing and harmful mental health terms have been used in past and present literature. Considering this, the authors have included such terms in search strategies to conduct a sensitive, comprehensive search for relevant studies. The authors of this review recognize and acknowledge the inappropriate and harmful nature of these terms, and note that the full search strategies include them, so that the reader can determine how they would like to proceed.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: February 22, 2024

Alerts: Monthly search updates until project completion

Search filters applied: Observational studies; real-world data studies

Limits

- Language limit: English-language

Table 6: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only

Syntax	Description
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.yr	Publication year

MEDLINE Strategy

1 exp Glucagon-Like Peptide 1/ or Receptors, Glucagon/ or Glucagon-Like Peptides/ or Glucagon-Like Peptide-1 Receptor/ or Glucagon-Like Peptide-1 Receptor Agonists/

2 ((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 analog*).ti,ab,kf.

3 ((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 (receptor? or protein?)).ti,ab,kf.

4 ((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 agonist*).ti,ab,kf.

5 (incretin mimetic* or GLP-1DA* or GLP1DA* or GLP 1RA* or GLP1RA*).ti,ab,kf.

6 (dulaglutide* or LY-2189265* or LY2189265* or Trulicity* or ly 05008* or ly05008*).ti,ab,kf.

7 exenatide/

8 (AC 2993 or AC 2993A or AC-2993 or AC002993 or AC2993 or AC2993A or baietta* or byetta* or bydureon* or DA 3091 or exenatide* or “exendin 4” or HSDB 7789 or LY 2148568 or LY2148568 or PT302 or Ex4 peptide* or ITCA 650 or ITCA650).ti,ab,kf.

9 Liraglutide/

10 (liraglutid* or HSDB 8205 or HSDB8205 or NN-2211 or NN2211 or NNC 90-1170 or NNC90-1170 or saxenda* or victoza* or xultophy*).ti,ab,kf.

11 (lixisenatide* or Adlyxin* or soliqua* or ZP10* or ZP 10 lyxumia* or “AVE 010” or AVE010 or “AVE 0010” or AVE0010).ti,ab,kf.

12 (semaglutide* or ozempic* or rybelsus* or wegovy* or NN 9535 or NN9535 or GTPL9724 or GTPL 9724).ti,ab,kf.

13 or/1-12

14 Mental health/ or exp Mental health services/ or exp Community Mental Health Centers/ or Mental health recovery/ or Mentally Ill Persons/

15 mental disorders/ or exp anxiety disorders/ or exp “bipolar and related disorders”/ or exp “disruptive, impulse control, and conduct disorders”/ or exp dissociative disorders/ or exp elimination disorders/ or exp “feeding and eating disorders”/ or exp mood disorders/ or motor disorders/ or neurotic disorders/ or exp paraphilic disorders/ or exp personality disorders/ or exp “schizophrenia spectrum and other psychotic disorders”/ or exp sexual dysfunctions, psychological/ or exp sleep wake disorders/ or exp

somatoform disorders/ or exp “trauma and stressor related disorders”/ or depression/ or Schizophrenia, Childhood/ or Anxiety, Separation/ or exp Self-Injurious Behavior/

16 (mental disorder* or mental health or mental disease* or mental illness* or posttraumatic or PTSD or PTD or trauma* or psychiat* or behavio?r disorder* or mood disorder* or affective disorder* or psycholog*).ti,ab,kf.

17 (anxiety or depress* or panic disorder* or neuro* or bipolar or schizophreni* or personality disorder* or psychosis or anorexia or eating disorder* or bulimia).ti,ab,kf.

18 (suicid* or parasuicid*).ti,ab,kf.

19 (self adj2 (injur* or mutilat* or inflict* or wound* or harm* or cut* or hurt* or destruct* or wound*)).ti,ab,kf.

20 or/14-19

21 Epidemiologic Methods/

22 exp Epidemiologic Studies/

23 Observational Studies as Topic/

24 Clinical Studies as Topic/

25 single-case studies as topic/

26 case reports as topic/

27 (Observational Study or Validation Studies or Clinical Study).pt.

28 (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

29 cohort*.ti,ab,kf.

30 (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.

31 ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.

32 ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.

33 (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.

34 ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.

35 (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

36 (population adj3 (study or studies or analysis or analyses)).ti,ab,kf.

37 (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

38 ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

39 (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.

40 ((natural adj experiment) or (natural adj experiments)).ti,ab,kf.

41 (quasi adj (experiment or experiments or experimental)).ti,ab,kf.

42 ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
43 (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.
44 or/21-43
45 Routinely collected health data/
46 Big data/
47 Databases, Factual/
48 National practitioner data bank/
49 Databases as Topic/
50 Decision Support Systems, Clinical/
51 Geographic Information Systems/
52 Health Information Systems/
53 exp Medical Records Systems, Computerized/
54 Datasets as Topic/
55 exp Records/
56 exp Registries/
57 exp Drug Prescriptions/
58 exp Drug Utilization/
59 Database Management Systems/
60 exp Data Mining/
61 (admin* adj2 (claim* or data* or record*)).ti,ab,kf.
62 adverse drug reaction reporting system*.ti,ab,kf.
63 big data*.ti,ab,kf.
64 (birth adj2 (certificate* or data* or record*)).ti,ab,kf.
65 ((claim or claims) adj2 data*).ti,ab,kf.
66 claims based.ti,ab,kf.
67 (data* adj2 (links or linked or linkage* or linking)).ti,ab,kf.
68 (data* adj2 (mining or mine or mined)).ti,ab,kf.
69 (data* adj2 repositor*).ti,ab,kf.
70 database management system*.ti,ab,kf.
71 dataset.pt.
72 (death adj2 (certificate* or data* or record*)).ti,ab,kf.
73 (dental adj2 (data* or record*)).ti,ab,kf.

74 discharge abstract*.ti,ab,kf.
75 ((diagnos* or discharg*) adj2 data*).ti,ab,kf.
76 factual data*.ti,ab,kf.
77 ((health or healthcare) adj3 (claim* or data* or record*)).ti,ab,kf.
78 (hospital* adj2 (data* or record*)).ti,ab,kf.
79 (inpatient* adj3 (data* or record*)).ti,ab,kf.
80 (insurance adj3 (claim* or data* or record*)).ti,ab,kf.
81 ((international or national or nationwide) adj3 (survey* or data*)).ti,ab,kf.
82 (managed care adj3 data*).ti,ab,kf.
83 medical record*.ti,ab,kf.
84 medical transcription data*.ti,ab,kf.
85 (medicare or medicaid).ti,ab,kf.
86 (nursing data* or nursing record*).ti,ab,kf.
87 (patient adj3 (data* or record*)).ti,ab,kf.
88 (billing* adj3 (record* or data*)).ti,ab,kf.
89 ((prescription* or prescrib*) adj3 (claim* or data* or record* or pattern*)).ti,ab,kf.
90 (real world adj5 (data* or evidence or research)).ab.
91 real world.ti,kf.
92 (registries or registry).ti,ab,kf.
93 ((register or registers) adj3 (link or links or linked or linkage* or linking or data*)).ti,ab,kf.
94 (routine* adj5 data*).ti,ab,kf.
95 ((utilization or utilisation) adj3 (data* or record* or pattern*)).ti,ab,kf.
96 participant data*.ti,ab,kf.
97 (real-life adj5 (data* or evidence or research)).ti,ab,kf.
98 physician claims.ti,ab,kf.
99 (Canadian Institute for Health Information or CIHI or “Centre for Health Services and Policy Research” or Health Council of Canada or Health Quality Council of Alberta or Institute for Clinical Evaluative Sciences or Manitoba Centre for Health Policy or “Newfoundland and Labrador Centre for Health Information” or Saskatchewan Health Quality Council or Statistics Canada or Public Health Agency of Canada).ti,ab,kf.
100 (Canadian Primary Care Sentinel Surveillance Network or Canadian Network of Observational Drug Effect Studies or CNODES or Canadian Chronic Disease Surveillance System or Registered persons database or Discharge Abstract Database or Discharge Abstracts Database or National Ambulatory Care Reporting System or NACRS or NPDUIS or National Prescription Drug Utilization Information System or National Physician Database or Home Care Reporting System or National Rehabilitation

Reporting System or Continuing Care Reporting System or Ontario Case Costing Initiative or OCCI).ti,ab,kf.

101 (Ontario Drug Benefit or Ontario Health Insurance Plan or Ambulatory Care Classification System or Regie de l'assurance maladie du Quebec or RAMQ or Non-Insured Prescription Drug Plan or Non-Insured Health Benefits).ti,ab,kf.

102 ((EMR or EMRs or EHR or EHRs) adj2 (data* or review* or analys*)).ti,ab,kf.

103 ((institutional or multiinstitutional) adj2 data*).ti,ab,kf.

104 exp medicare/sn

105 medicaid/sn

106 or/45-105

107 13 and 20 and 44

108 13 and 20 and 106

109 107 or 108

110 limit 109 to English

Embase Strategy

1 exp *glucagon like peptide 1 receptor agonist/ or glucagon like peptide receptor agonist/ or glucagon like peptide/ or glucagon like peptide receptor/

2 ((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 analog*).ti,ab,kf,dq.

3 ((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 (receptor? or protein?)).ti,ab,kf,dq.

4 ((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 agonist*).ti,ab,kf,dq.

5 (incretin mimetic* or GLP-1DA* or GLP1DA* or GLP 1RA* or GLP1RA*).ti,ab,kf,dq.

6 (dulaglutide* or LY-2189265* or LY2189265* or Trulicity* or ly 05008* or ly05008*).ti,ab,kf,dq.

7 (AC 2993 or AC 2993A or AC-2993 or AC002993 or AC2993 or AC2993A or baietta* or byetta* or bydureon* or DA 3091 or exenatide* or “exendin 4” or HSDB 7789 or LY 2148568 or LY2148568 or PT302 or Ex4 peptide* or ITCA 650 or ITCA650).ti,ab,kf,dq.

8 (liraglutid* or HSDB 8205 or HSDB8205 or NN-2211 or NN2211 or NNC 90-1170 or NNC90-1170 or saxenda* or victoza* or xultophy*).ti,ab,kf,dq.

9 (lixisenatide* or Adlyxin* or soliqua* or ZP10* or ZP 10 lyxumia* or “AVE 010” or AVE010 or “AVE 0010” or AVE0010).ti,ab,kf,dq.

10 (semaglutide* or ozempic* or rybelsus* or wegovy* or NN 9535 or NN9535 or GTPL9724 or GTPL 9724).ti,ab,kf,dq.

11 or/1-10

12 mental health care/ or mental health service/ or mental health/ or mental disease/ or adjustment disorder/ or alexithymia/ or exp anxiety disorder/ or complicated grief/ or exp dissociative disorder/ or exp emotional disorder/ or exp experimental mental disease/ or hikikomori/ or exp mental deficiency/

or mental infantilism/ or mental instability/ or mental overstimulation/ or exp mood disorder/ or exp neurosis/ or organic brain syndrome/ or organic psychosyndrome/ or exp personality disorder/ or psychiatric complication/ or exp psychosexual disorder/ or exp psychosis/ or exp psychosomatic disorder/ or exp psychotrauma/ or exp schizophrenia spectrum disorder/ or stupor/ or exp suicidal behavior/ or exp eating disorder/

13 (mental disorder* or mental health or mental disease* or mental illness* or posttraumatic or PTSD or PTD or trauma* or psychiat* or behavio?r disorder* or mood disorder* or affective disorder* or psycholog*).ti,ab,kf,dq.

14 (anxiety or depress* or panic disorder* or neuro* or bipolar or schizophreni* or personality disorder* or psychosis or anorexia or eating disorder* or bulimia).ti,ab,kf,dq.

15 (suicid* or parasuicid*).ti,ab,kf,dq.

16 (self adj2 (injur* or mutilat* or inflict* or wound* or harm* or cut* or hurt* or destruct* or wound*)).ti,ab,kf,dq.

17 or/12-16

18 observational study/

19 cohort analysis/

20 longitudinal study/

21 follow up/

22 retrospective study/

23 exp case control study/

24 cross-sectional study/

25 quasi experimental study/

26 prospective study/

27 (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

28 cohort*.ti,ab,kf.

29 (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.

30 ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.

31 ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.

32 (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.

33 ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.

34 (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

35 (population adj3 (study or studies or analysis or analyses)).ti,ab,kf.

36 (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

37 ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

38 (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.

39 ((natural adj experiment) or (natural adj experiments)).ti,ab,kf.

40 (quasi adj (experiment or experiments or experimental)).ti,ab,kf.

41 ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

42 (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.

43 or/18-42

44 Routinely collected health data/

45 Big data/

46 Databases, Factual/

47 National practitioner data bank/

48 Databases as Topic/

49 Decision Support Systems, Clinical/

50 Geographic Information Systems/

51 Health Information Systems/

52 exp Medical Records Systems, Computerized/

53 Datasets as Topic/

54 exp Records/

55 exp Registries/

56 exp Drug Prescriptions/

57 exp Drug Utilization/

58 Database Management Systems/

59 exp Data Mining/

60 (admin* adj2 (claim* or data* or record*)).ti,ab,kf.

61 adverse drug reaction reporting system*.ti,ab,kf.

62 big data*.ti,ab,kf.

63 (birth adj2 (certificate* or data* or record*)).ti,ab,kf.

64 ((claim or claims) adj2 data*).ti,ab,kf.

65 claims based.ti,ab,kf.

66 (data* adj2 (links or linked or linkage* or linking)).ti,ab,kf.

67 (data* adj2 (mining or mine or mined)).ti,ab,kf.

68 (data* adj2 repositor*).ti,ab,kf.
69 database management system*.ti,ab,kf.
70 dataset.pt.
71 (death adj2 (certificate* or data* or record*)).ti,ab,kf.
72 (dental adj2 (data* or record*)).ti,ab,kf.
73 discharge abstract*.ti,ab,kf.
74 ((diagnos* or discharg*) adj2 data*).ti,ab,kf.
75 factual data*.ti,ab,kf.
76 ((health or healthcare) adj3 (claim* or data* or record*)).ti,ab,kf.
77 (hospital* adj2 (data* or record*)).ti,ab,kf.
78 (inpatient* adj3 (data* or record*)).ti,ab,kf.
79 (insurance adj3 (claim* or data* or record*)).ti,ab,kf.
80 ((international or national or nationwide) adj3 (survey* or data*)).ti,ab,kf.
81 (managed care adj3 data*).ti,ab,kf.
82 medical record*.ti,ab,kf.
83 medical transcription data*.ti,ab,kf.
84 (medicare or medicaid).ti,ab,kf.
85 (nursing data* or nursing record*).ti,ab,kf.
86 (patient adj3 (data* or record*)).ti,ab,kf.
87 (billing* adj3 (record* or data*)).ti,ab,kf.
88 ((prescription* or prescrib*) adj3 (claim* or data* or record* or pattern*)).ti,ab,kf.
89 (real world adj5 (data* or evidence or research)).ab.
90 real world.ti,kf.
91 (registries or registry).ti,ab,kf.
92 ((register or registers) adj3 (link or links or linked or linkage* or linking or data*)).ti,ab,kf.
93 (routine* adj5 data*).ti,ab,kf.
94 ((utilization or utilisation) adj3 (data* or record* or pattern*)).ti,ab,kf.
95 participant data*.ti,ab,kf.
96 (real-life adj5 (data* or evidence or research)).ti,ab,kf.
97 physician claims.ti,ab,kf.
98 (Canadian Institute for Health Information or CIHI or “Centre for Health Services and Policy Research” or Health Council of Canada or Health Quality Council of Alberta or Institute for Clinical Evaluative Sciences or Manitoba Centre for Health Policy or “Newfoundland and Labrador Centre for Health

Information" or Saskatchewan Health Quality Council or Statistics Canada or Public Health Agency of Canada).ti,ab,kf.

99 (Canadian Primary Care Sentinel Surveillance Network or Canadian Network of Observational Drug Effect Studies or CNODES or Canadian Chronic Disease Surveillance System or Registered persons database or Discharge Abstract Database or Discharge Abstracts Database or National Ambulatory Care Reporting System or NACRS or NPDUIS or National Prescription Drug Utilization Information System or National Physician Database or Home Care Reporting System or National Rehabilitation Reporting System or Continuing Care Reporting System or Ontario Case Costing Initiative or OCCI).ti,ab,kf.

100 (Ontario Drug Benefit or Ontario Health Insurance Plan or Ambulatory Care Classification System or Regie de l'assurance maladie du Quebec or RAMQ or Non-Insured Prescription Drug Plan or Non-Insured Health Benefits).ti,ab,kf.

101 ((EMR or EMRs or EHR or EHRs) adj2 (data* or review* or analys*)).ti,ab,kf.

102 ((institutional or multiinstitutional) adj2 data*).ti,ab,kf.

103 [exp medicare/sn]

104 [medicaid/sn]

105 or/44-104

106 11 and 17 and 43

107 11 and 17 and 105

108 106 or 107

109 limit 108 to english

110 109 not (conference abstract or conference review).pt.

111 109 and (conference abstract or conference review).pt.

Appendix 2: Summary of Evidence in Meta-Analysis of Randomized Controlled Trials

Note that this appendix has not been copy-edited.

Suicidal ideation, self-harm, and suicide were not prespecified safety end points in randomized controlled trials of GLP-1 RAs. To date, only 1 meta-analysis was conducted using data from such trials to determine whether the use of GLP-1 RAs was associated with an imbalance in psychiatric events among trials with a treatment duration of at least 52 weeks.[24] The meta-analysis included 31 trials, of which 22 were for the treatment of type 2 diabetes, and 9 were for the treatment of obesity. Approximately 45,000 GLP-1 RAs and 40,000 patients on comparators were included across the 31 trials. Eight of the 31 randomized controlled trials were large with more than 1,000 patients per arm. Overall, the incidence of psychiatric adverse events and suicidal behaviour was not found to be associated with GLP-1 RA treatment, with pooled ORs of 0.97 (95% CI, 0.83 to 1.15) and 0.86 (95% CI, 0.47 to 1.56), respectively. Results remained consistent in multiple subgroup and sensitivity analyses, including stratification by individual drug, indication, and trial duration. There was also no evidence of an association between GLP-1 RA use and depression (pooled OR = 0.96; 95% CI, 0.68 to 1.35) or anxiety (pooled OR = 0.88; 95% CI, 0.51 to 1.52). The grade of evidence was moderate for all 4 outcomes.

Comment: Given that self-harm and suicide are relatively rare events, randomized controlled trials are often underpowered to detect these outcomes. Indeed, the adverse events reported did not include suicides and included general psychiatric adverse events. Most trials included in the meta-analysis had durations of 1 to 2 years, and many excluded patients with moderate to severe mental illness, which further limits the number of events that are observed. Furthermore, none of the trials included psychiatric adverse events as predefined study end points, which may have led to incomplete reporting. Data were retrieved first through the primary trial publication and missing data were then identified through secondary trial publications and the clinicaltrials.gov registry, which contains unadjudicated data. Finally, the trials may have reduced generalizability due to their highly selected populations, stringency of follow-up, and high levels of medication adherence. Although trial data have high internal validity, it is necessary to supplement these data with real-world evidence.

Appendix 3: Summary of Evidence in Pharmacovigilance Studies

Note that this appendix has not been copy-edited.

Three studies used the US FDA Adverse Event Reporting System (database of voluntary reporting of adverse events) to conduct disproportionality analyses for GLP-1 RAs and self-harm and suicidal ideation. When comparing GLP-1 RAs to all other drugs between 2005 and 2023, suicide and self-injury were not reported more than other adverse events (reporting OR = 0.16; 95% CI, 0.15 to 0.18).[25] Similar results were found for a 2018 to 2022 analysis with Bayesian Information Component (IC_{025}) values of less than 0 for each of the GLP-1 RAs individually.[26] When comparing GLP-1 RAs to metformin and insulin between 2005 and 2023, disproportionate reporting of suicidal ideation and "depression/suicidal" was observed for semaglutide and liraglutide, but not for dulaglutide, exenatide, lixisenatide, or tirzepatide; no disproportionate reporting of suicidal behaviour, suicide attempt, or completed suicide was observed for any of the GLP-1 RAs.[27] Meanwhile, a comparative safety analysis using the European EudraVigilance database compared the reporting probability of suicidal events between the different GLP-1 RAs and found that these were mostly reported among users of semaglutide and liraglutide compared to users of exenatide and dulaglutide.[6]

Comment: Though useful for signal generation, pharmacovigilance analyses are subject to significant limitations, which include incomplete capturing of events, absence of information of the number of exposed subjects (no denominator), and inability to control for confounding variables. Significant media attention has been paid to GLP-1 RAs in recent years and may have led to increased reporting compared to other medications. Furthermore, there are well-known associations between type 2 diabetes, obesity, depression, and suicidality.[7,8,12,28-30] Confounding by indication and protopathic bias are likely present in these studies, and their results should be considered with caution.

Appendix 4: Abstracts of Other Randomized and Controlled Clinical Trials of Interest

O'Neil PM, Aroda VR, Astrup A, et al. Neuropsychiatric safety with liraglutide 3.0 mg for weight management: Results from randomized controlled phase 2 and 3a trials. Diabetes Obes Metab. 2017 11;19(11):1529-1536. PubMed

Appendix 5: Abstracts of Other Observational Studies of Interest

Bae JH, Lee H, Bea S, Shin JY. Liraglutide and unexpected psychiatric adverse events in patients with obesity: A pharmacovigilance study with machine learning approach. *Pharmacoepidemiol Drug Saf*. 2022 September;31(Supplement 2):37-38.

Cavanaugh J, Hon S. Watch for high tides, but maybe at home: GLP-1 receptor agonist exposures reported to NPDS. *Clin Toxicol*. 2022;60(Supplement 2):134.

Tobaiqy M, Elkout H. Psychiatric adverse events associated with semaglutide, liraglutide and tirzepatide: a pharmacovigilance analysis of individual case safety reports submitted to the EudraVigilance database. *Int J Clin Pharm*. 2024 Jan 24;24:24. PubMed

Arillotta D, Floresta G, Guirguis A, et al. GLP-1 Receptor Agonists and Related Mental Health Issues; Insights from a Range of Social Media Platforms Using a Mixed-Methods Approach. Brain Sciences. 2023 November;13(11) (no pagination).

For more information on CoLab and its work, visit **colab.cadth.ca**

Canada's Drug and Health Technology Agency

CoLab Network

This appraisal was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) through the Post Market Drug Evaluation CoLab Network. This work was supported by CADTH and its Post-Market Drug Evaluation Program, through funding provided by Health Canada.