
A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer

Alves C, Batel-Marques F, Macedo AF

CRD summary

The review found that the available published evidence was insufficient to support an increased risk of acute pancreatitis or cancer associated with GLP-1 agonist use in patients with type 2 diabetes. These conclusions appear to be a reliable reflection of the available published data.

Authors' objectives

To evaluate the risk of developing acute pancreatitis or cancer in patients with type 2 diabetes taking a GLP-1 agonist (exenatide or liraglutide).

Searching

MEDLINE, EMBASE, The Cochrane Library and ClinicalTrials.gov were searched to May 2012 for studies published in English; search strategies were reported in an additional file. Reference lists of relevant studies were searched.

Study selection

Randomised controlled trials (RCTs), case-control studies and cohort studies of at least 12 weeks duration in patients of any age with type 2 diabetes mellitus were eligible for inclusion. Studies had to compare a GLP-1 agonist with placebo or an active control (oral hypoglycaemic agents or insulin) and present effect estimates on acute pancreatitis or cancer associated with GLP-1 agonist use.

Most studies were conducted in populations with diabetes not controlled with metformin. Mean population ages varied; most were between 40 and 60 years. Studies compared GLP-1 agonists to placebo or other anti-diabetic drugs. Some studies also compared different doses of the same GLP-1 agonist and some compared exenatide with liraglutide. Treatment duration in the RCTs ranged from 12 to 104 weeks (24 or 26 weeks in around half the studies). Cohort studies ranged from 76 to 212 weeks in duration.

The authors did not state how many reviewers selected studies.

Assessment of study quality

Study quality was assessed using the Downs and Black checklist. Study quality was then judged to be high (scores ≥ 20), moderate (scores from 10 to 19) or low (scores < 10).

Two reviewers independently assessed study quality. Disagreements were resolved by discussion with a third reviewer.

Data extraction

Data on the incidence of acute pancreatitis, any cancer and thyroid cancer were extracted in order to calculate odds ratios with 95% confidence intervals. Data were added in studies with multiple intervention or control treatments.

The authors did not state how many reviewers extracted data.

Methods of synthesis

Meta-analyses were performed to calculate pooled odds ratios with 95% confidence intervals using a random effects model. Where no events were reported in one or both groups, a continuity correction of 0.5 was added to each cell. Heterogeneity was assessed using the I^2 statistic and X^2 test. Publication bias was evaluated by visual examination of funnel plots and by Egger's test. Sensitivity analyses were conducted to explore the influence of study design, methodological quality score, type of comparator and GLP-1 agonist dose regimens (weekly or daily).

Results of the review

Twenty-five studies were included: 22 RCTs (sample size range 54 to 1,087) and three retrospective cohort studies, all

of exenatide (sample size range 22,789 to 482,034). Study quality was considered high in 15 studies and moderate in 10 studies (scores ranged from 13 to 25).

Acute pancreatitis: Neither exenatide (13 studies) nor liraglutide (12 RCTs) were associated with increased incidence of acute pancreatitis. Sensitivity analyses yielded similar results. There was evidence for publication bias in the analysis of the 10 exenatide RCTs.

Any cancer: In the main analyses neither exenatide (10 RCTs) nor liraglutide (10 RCTs) were associated with increased incidence of cancer. Sensitivity analyses showed similar results for exenatide but liraglutide was associated with a statistically significant increased risk of cancer when only the five high quality studies were analysed (OR 2.60, 95% CI 1.08 to 6.27; $I^2=0%$); neither the comparator treatments nor the number of cancers were explicitly stated for this analysis (although it appeared the comparators were other anti-diabetic drugs).

Thyroid cancer: There were no cases of thyroid cancer in patients taking exenatide. Liraglutide was not significantly associated with increased incidence of thyroid cancer.

Authors' conclusions

Current available published evidence was insufficient to support an increased risk of acute pancreatitis or cancer associated with GLP-1 agonists.

CRD commentary

The review addressed a clear question and was supported by reproducible eligibility criteria. Several relevant electronic databases were searched. The restriction to identifying only studies published in English means that some relevant data may have been missed. Duplicate processes were employed to reduce the risks of reviewer error and bias during the study quality assessments; the authors did not report on whether such methods were used during study selection or data extraction.

Study quality was assessed and the results were used for sensitivity analyses. Appropriate methods were used to pool data and to assess and investigate heterogeneity. The authors acknowledged that they did not attempt to seek out unpublished data and added that none of the randomised trials were designed to prospectively monitor for cancer incidence.

The authors' conclusions appear to be a reliable reflection of the available published data.

Implications of the review for practice and research

Practice: The authors stated that physicians and patients should remain vigilant for episodes of acute pancreatitis or cancer and report any events to the appropriate pharmacovigilance system.

Research: The authors stated a need for long-term well-designed epidemiological studies assessing the cancer and acute pancreatitis risk associated with GLP-1 agonists.

Funding

Foundation for Science and Technology (FCT), Portugal.

Bibliographic details

Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Research and Clinical Practice* 2012; 98(2): 271-284

PubMedID

23010561

DOI

10.1016/j.diabres.2012.09.008

Original Paper URL

<http://www.sciencedirect.com/science/article/pii/S0168822712003129>

Indexing Status

Subject indexing assigned by NLM

MeSH

Diabetes Mellitus, Type 2 /drug therapy; Glucagon-Like Peptide 1 /adverse effects /agonists /analogs & derivatives /therapeutic use; Humans; Hypoglycemic Agents /adverse effects /therapeutic use; Liraglutide; Neoplasms /chemically induced; Pancreatitis /chemically induced; Peptides /adverse effects /therapeutic use; Venoms /adverse effects /therapeutic use

AccessionNumber

12013001788

Date bibliographic record published

20/02/2013

Date abstract record published

19/11/2013

Record Status

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.