Systematic review protocol and data-analysis plan

A systematic review of the placebo effect of GLP-1 receptor agonists versus new class oral glucose-lowering agents in type 2 diabetes

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This systematic review and meta-analysis will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[1,2] Methods of the analysis and inclusion criteria are pre-specified and documented in this protocol, and will be registered at the International prospective register of systematic reviews (PROSPERO; accessible through http://www.crd.york.ac.uk/PROSPERO/).

Background and aim

Every treatment is associated with a placebo-effect, which has been a focus for research for many years, especially in the area of pain relief. One of the determinants of the placebo-effect is the route of drug-administration. In migraine treatment, for example, sham surgery or sham acupuncture resulted in higher responder ratios than oral placebos.[3] The role of the placebo-effect in different type 2 diabetes (T2DM) treatments is completely unknown. In the past decade, a number of new T2DM treatments have been introduced: the oral dipeptidyl peptidase-4 (DPP-4) inhibitors have no effect on weight, while the injectable glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are associated with weight loss. Next, the new class of the oral sodium-glucose co-transporter 2 (SGLT2) inhibitors are also reported to decrease body weight. We hypothesize that GLP-1 RAs, DPP-4 inhibitors as well as SGLT-2 inhibitors are associated with a placebo-effect regarding weight, HbA1c and adverse events, and that the placebo-effect of injectable GLP-1 RAs exceeds that of oral drugs, particularly the DPP-4 inhibitors. We will test this hypothesis in a systematic review, with an analysis of pooled data, directly comparing the placebo-effect of GLP-1 RAs and DPP-4 inhibitors with SGLT2-inhibitors as intermediate, in diabetes treatment efficacy, as assessed by weight change, improvement in glycaemic control, and adverse events, including hypoglycaemia.

Literature search methodology

A literature search will be conducted in PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (Central), without restrictions regarding language or year of

publication. The last search update will be on August 31, 2014.

Combined text and Medical Subject Heading terms will be used, using search terms on:

1. The substance names of GLP-1 RAs: exenatide, liraglutide, lixisenatide, exenatide QW, dulaglutide, albiglutide, taspoglutide (semaglutide)
2. The substance names of DPP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin, (alogliptin, linagliptin, dutogliptin)
3. The substance names of SGLT-2 inhibitors: dapagliflozin, canagliflozin, empagliflozin, (ertugliflozin)
4. Randomized controlled trial. The sensitivity-maximizing version of the Cochrane Highly Sensitive Search Strategy for RCT's[4] will be applied.
5. Diabetes (mellitus)
6. Placebo or double-blind method

The complete search strategy that will be used for PubMed is described in appendix 1; for EMBASE in appendix 2; for the Cochrane library in appendix 3. We will seek advice from a medical librarian regarding the search strategy.

Study selection and eligibility criteria

Studies will be considered eligible for inclusion if they are placebo-controlled randomized clinical trials; with a study duration of 24 to 30 weeks, i.e. administration of placebo or active drug for 24 to 30 weeks, or, with longer study duration and reporting of data on 24 to 30 weeks of follow-up (because effects are likely to occur within this timeframe; most studies have a follow-up duration of 24-30 weeks; and in order to be able to compare studies of the same duration); and conducted in adult patients with type 2 diabetes aged 18 years or older, who don't receive any background diabetes medication or who are treated with a maximum of two of the following medications: metformin (any dose), sulfonylurea (any dose) or thiazolidinediones (any dose); and are randomized between the addition of either a GLP-1 analogue (exenatide [bid or once weekly], liraglutide, lixisenatide, dulaglutide, albiglutide,

semaglutide, taspoglutide) or placebo; a DPP-4 inhibitor (sitagliptin, vildagliptin, linagliptine, saxagliptin, alogliptin, linagliptin) or placebo; or a SGLT-2 inhibitor (dapagliflozin, canagliflozin, empagliflozin, ertugliflozin) or placebo. Studies will be included only if they report (changes in) HbA1c or weight, and if either (changes in) HbA1c or weight are reported as primary endpoints, because the primary aim of this meta-analysis is to evaluate the effect of placebo on weight and HbA1c, the cornerstones of diabetes treatment efficacy.

Exclusion criteria will be: observational and retrospective studies, no data available on 24 to 30 weeks of follow-up, studies in which placebo is started together with active antidiabetic medication or interventions, such as lifestyle measures (in order to study the 'true' placebo effect), studies in which multiple kinds of placebo are given at the same time to study subjects ('double dummy'; in order to be able to clearly identify to what drug the corresponding placebo is linked), studies in which multiple antidiabetic agents of different classes are linked to the same placebo (in order to clearly identify to what drug the corresponding placebo is linked), and studies conducted in participants receiving insulin or background diabetes medication other than metformin and/or sulfonylurea and/or or thiazolidinediones, such as glinides, amylin agonists or alpha-glucosidase inhibitors (acarbose), because these drugs have not been widely adopted in clinical practice.

Only published trials will be included. If the study is eligible, without an available full text version, the corresponding author will be emailed to obtain data. If important parameters are missing, authors will also be emailed to obtain data. In case of multiple reports or companion papers of the same study, outcome data from the original study will be extracted, unless the first report was a planned interim analysis.

When both data from intention to treat (ITT; all randomized patients), or modified ITT (all randomized patients who received at least one dose of allocated treatment and had at least one post-baseline measurement), and per protocol (PP) analyses are reported: (m)ITT data will be extracted from the published paper.

Data extraction

After conducting the search strategy in PubMed, EMBASE and the Cochrane Library, two authors (MtG and HdW) will independently examine each title and abstract to exclude obviously irrelevant reports. Kappa statistic will be calculated for measuring agreement between the two authors; disagreements will be resolved by a third investigator (CT). Publications retrieved from PubMed, EMBASE, and the Cochrane Library will be imported in a reference management software (www.endnote.com). After removing duplicate results, two authors (MtG and HdW) will independently examine each full-text report to determine eligibility. After trial inclusion, information will be extracted by MtG according to a pre-defined spreadsheet and compared independently by HdW. Disagreements between reviewers on trial eligibility or data extraction will be resolved by consensus after consultation of a third reviewer (CT). Information will be extracted from each included study on: (1) trial characteristics (author identification, trial registration, year of publication) (2) characteristics of the trial population (sample size, age, sex, ethnicity, specific comorbidity, baseline HbA1c, body weight, BMI, diabetes duration, background diabetes therapy) (3) trial interventions (including dose, duration of intervention and percentage drop-out in interventional and placebo group); (4) pre-specified outcome measures for the placebo-group and intervention group (mean [SD] change in body weight; mean [SD] change in HbA1c; and number of patients with adverse events, and hypoglycaemia, with severe hypoglycaemia defined as when treatment by a third party is necessary). In case of multiple intervention groups within the same study, only the active drug to which the corresponding placebo is linked will be included in the analysis, and different doses of the same active drug will be combined into one active comparator group, according to the Cochrane handbook.[4]

Assessment of risk of bias

The Cochrane Collaboration's risk of bias tool,[4] will be used to asses risk of bias in individual studies in random sequence generation, concealment of allocation, blinding of participants

and personnel, completeness of main outcome data (because of a high rate of discontinuation, type of analysis, or imputation of missing data), selective reporting, and other forms of bias (including extent of loss to follow-up, premature termination of the trial and analysis according to intention-to-treat). The risk of bias of all six domains will be regarded high in case of the presence of high bias in any domain, low if all key domains (all domains except random sequence generation and allocation concealment) are of low bias, and unclear in all other cases.[4] When only the risk of bias in the seventh domain (other bias) is unclear it will be regarded as low risk of bias.[4] The risk of bias will be assessed independently and unblinded by two authors (HdW and MtG), when necessary consensus will be determined through help of a third author (CT).

Data synthesis and analysis

The primary endpoint will be the change in body weight from baseline until end of follow-up with the placebo of GLP-1 RAs and the placebo of DPP-4 inhibitors, and its difference between these two drug classes. Based on clinical reasoning, a distinction will be made for short-acting (once or twice daily) and long-acting (once weekly) GLP-1 RAs using subgroup analyses. Analogous to clinical efficacy, we expect the placebo-effect of SGLT-2 inhibitors regarding weight change to lie between the placebo-effect of GLP-1 RAs and DPP-4 inhibitors; and will therefore also be evaluated, as an intermediate. We choose change in body weight as a primary endpoint, as we expect it to change most with placebo treatment, and as it is equally important to HbA1c in evaluating diabetes treatment efficacy; HbA1c will change along with weight during diabetes treatment.

Second, the change in HbA1c from baseline until end of follow-up and the incidence of adverse events, including hypoglycaemia and percentage of drop-out due to adverse events will be evaluated and described. Again, the placebo-effect of GLP-1 RAs will be shown against the placebo-effect of DPP-4 inhibitors, with SGLT2-inhibitors as intermediate.

Weight and HbA1c will be analyzed as continuous variables, absolute differences between

arithmetic means before and after interventions will be reported. For the proportion of patients experiencing adverse events or hypoglycaemia, mean differences will be calculated. Mean differences between the placebo group and all active comparator groups with standard deviations (SD's) and/or 95% confidence intervals will be calculated for continuous outcomes using an inverse variance random effects model. If a specific study doesn't report standard deviations, this will be calculated from the standard error and the sample size or the 95% confidence interval (CIs).

We will test for statistical heterogeneity with the I^2 test; I^2 values of 50-75% and over 75% represent substantial and considerable heterogeneity, respectively.[4] Potential causes of heterogeneity will be explored by looking at outliers and by performing sensitivity analyses, excluding reports with high overall risk of bias. Sensitivity analyses are planned for every outcome based on its overall risk of bias. For each trial, publication bias will be assessed for the primary outcome weight change both graphical, by a funnel plot, displaying the effect by the inverse of its standard error; and formally with Egger's test,[5] to see if the effect will decrease with increasing sample size. All analyses will be performed using RevMan 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

Subgroup and sensitivity analyses

Subgroup analyses will be performed based on different background medication, baseline weight of the trial population, age of the trial population (adult versus elderly), ethnicity of the trial population (Asian, Caucasian or black, when applicable), specific comorbidity (such as renal impairment) and baseline HbA1c. We will make a distinction between the short-acting (once or twice daily: exenatide, liraglutide, lixisenatide) and long-acting (once weekly: exenatide QW, dulaglutide, albiglutide, taspoglutide, semaglutide) GLP-1 RAs using sensitivity analyses. Also, sensitivity analyses will be performed according to the efficacy of the corresponding active drug, regarding weight, HbA1c and adverse effects.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of clinical epidemiology 2009;62:1006-12.

2. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology 2009;62:e1-34.

3. Meissner K, Fassler M, Rucker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. JAMA internal medicine 2013;173:1941-51.

4. Higgins J, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions. In: The Cochrane Collaboration; 2011.

5. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315:629-34.

6. Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association : JMLA 2006;94:41-7.

Appendix 1: PubMed search strategy

1. Exenatide[nm]
2. Exenatide*[tw]
3. Liraglutide[nm]
4. Liraglutide*[tw]
5. Lixisenatide[nm]
6. Lixisenatide*[tw]
7. Dulaglutide[nm]
8. Dulaglutide*[tw]
9. Albiglutide[nm]
10. Albiglutide*[tw]
11. Taspoglutide[nm]
12. Taspoglutide*[tw]
13. Semaglutide*[tw]
14. Sitagliptin[nm]
15. Sitagliptin*[tw]
16. Vildagliptin[nm]
17. Vildagliptin*[tw]
18. Saxagliptin[nm]
19. Saxagliptin*[tw]
20. Alogliptin[nm]
21. Alogliptin*[tw]
22. Linagliptin[nm]
23. Linagliptin*[tw]
24. Dutogliptin[nm]
25. Dutogliptin*[tw]
26. Dapagliflozin[nm]
27. Dapagliflozin*[tw]
28. Canagliflozin[nm]
29. Canagliflozin*[tw]
30. Empagliflozin[nm]
31. Empagliflozin*[tw]
32. Ertugliflozin*[tw]
33. OR #1-32
34. randomized controlled trial[pt]
35. controlled clinical trial[pt]
36. randomized[tiab]
37. placebo[tiab]
38. drug therapy[sh]
39. randomly[tiab]
40. trial[tiab]
41. groups[tiab]
42. OR #34-41
43. animals[mh] NOT humans[mh]
44. #42 NOT #43
45. diabet*[tw]
46. Diabetes Mellitus[mh]
47. #45 OR #46
48. Placebo*[tw]
49. Double-Blind Method [mh]
50. #48 OR #49
51. #33 AND #44 AND #47 AND #50

Appendix 2: EMBASE search strategy

1. Exenatide.mp. or Exenatide*.ti,ab. or Liraglutide.mp. or Liraglutide*.ti,ab. or Lixisenatide.mp. or Lixisenatide*.ti,ab. or Dulaglutide.mp. or Dulaglutide*.ti,ab. or Albiglutide.mp. or Albiglutide*.ti,ab. or Taspoglutide.mp. or Taspoglutide*.ti,ab. or Semaglutide.mp. or Semaglutide*.ti,ab. or Sitagliptin.mp. or Sitagliptin*.ti,ab. or Vildagliptin.mp. or Vildagliptin*.ti,ab. or Saxagliptin.mp. or Saxagliptin*.ti,ab. or Alogliptin.mp. or Alogliptin*.ti,ab. or Linagliptin.mp. or Linagliptin*.ti,ab. or Dutogliptin.mp. or Dutogliptin*.ti,ab. or Dapagliflozin.mp. or Dapagliflozin*.ti,ab. or Canagliflozin.mp. or Canagliflozin*.ti,ab. or Empagliflozin.mp. or Empagliflozin*.ti,ab. or Ertugliflizon.mp. or Ertugliflozin*.ti,ab.
2. (random* or double-blind*).tw
3. Placebo.mp.
4. 2 or 3 [Wong 2006, best optimization of sensitivity and specificity for RCTs[6]]
5. Diabetes mellitus.sh.
6. Diabet*.tw.
7. 5 or 6
8. Placebo*.tw.
9. Double-blind.mp
10. 8 or 9
11. 1 and 4 and 7 and 10
12. limit 11 to conference abstract
13. 11 not 12

Appendix 3: search strategy for The Cochrane library

1. Exenatide* or Liraglutide* or Lixisenatide* or Dulaglutide* or Albiglutide* or Taspoglutide* or Semaglutide* or Sitagliptin* or Vildagliptin* or Saxagliptin* or Alogliptin* or Linagliptin* or Dutogliptin* or Dapagliflozin* or Canagliflozin* or Empagliflozin* or Ertugliflozin*:ti,ab,kw
2. Placebos (MeSH)
3. random* or double-blind*:ti,ab,kw
4. 2 or 3
5. Diabetes Mellitus (MeSH)
6. Diabet*:ti,ab,kw
7. 5 or 6
8. Placebo*:ti,ab,kw
9. Double-blind method (MeSH)
10. 8 or 9
11. 1 and 4 and 7 and 10
12. Limit #11 to Trials