**Appendix 1.** Search strategy

**Cochrane Library  Issue 6 2015**

**Search Name:Antihyperglycemics review**

**Last Saved:17/07/2015 14:06:03.665**

**Description:**

IDSearch

#1[mh "Diabetes Mellitus"]

#2[mh "Diabetes Mellitus, Type 2"]

#3[mh "Diabetes Mellitus, Type 1"]

#4[mh "insulin resistance"]

#5[mh "glucose intolerance"]

#6(MODY or NIDDM or T2DM):ti,ab

#7(non insulin\* depend\* or noninsulin\* depend\* or noninsulin depend\* or noninsulin depend\*):ti,ab

#8(insulin\* depend\* or insulin\* depend\* or insulin depend\* or insulin depend\*):ti,ab

#9((keto\*resist\* or non\*keto\*) near/3 diabet\*):ti,ab

#10(((late or adult\* or matur\* or slow or stabl\*) near/3 onset) and diabet\*):ti,ab

#11{or #1-#10}

#12[mh "Dose-Response Relationship, Drug"]

#13[mh "Drug Administration Schedule"]

#14[mh "Drug Substitution"]

#15((down or drug or dose) near/3 titrat\*):ti,ab

#16((drug or dose) near/3 reduc\*):ti,ab

#17((drug or dose) near/3 de-escalation):ti,ab

#18((drug or dose) near/3 taper$):ti,ab

#19(discontinu\*):ti

#20(withdraw\*):ti

#21(stop\* or spac\*):ti

#22(ceas\* or cessation):ti,ab

#23(interval near/3 widening):ti,ab

#24(deprescri\* or de-prescri\*):ti,ab

#25(interval near/3 spacing):ti,ab

#26discontinu\*:ti

#27eliminat\*:ti

#28reduc\*.ti

#29{or #12-#28}

#30#11 and #29

#31[mh "Hypoglycemic Agents"]

#32(antihyperglycemic or anti-hypergylcemic):ti,ab

#33[mh Metformin]

#34[mh "Sulfonylurea Compounds"]

#35(Meglitinides or Sulfonylurea):ti,ab

#36[mh Glyburide]

#37(glyburide\*):ti,ab

#38[mh Thiazolidinediones]

#39(Glitazones or TZD\*):ti,ab

#40[mh "Dipeptidyl-Peptidase IV Inhibitors"]

#41[mh "Glucagon-Like Peptide 1"]

#42[mh Insulin]

#43[mh "Insulin, Long-Acting"]

#44[mh "Insulin, Short-Acting"]

#45{or #31-#44}

#46#30 and #45

**Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>**

Search Strategy:

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1     Diabetes Mellitus/dt (13584)

2     Diabetes Mellitus, Type 2/dt (22806)

3     Diabetes Mellitus, Type 1/dt (11593)

4     (renal adj insufficiency).ti. (6496)

5     (impaired glucos$ toleranc$ or glucos$ intoleranc$ or insulin resistan$).ti. (20591)

6     (MODY or NIDDM or T2DM).ti,ab. (16197)

7     (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or noninsulin?depend$).ti,ab. (12040)

8     (insulin$ depend$ or insulin$ depend$ or insulin?depend$ or insulin?depend$).ti. (10989)

9     ((typ? 2 or typ? II or typ?2 or typ?II) adj diabet$).ti,ab. (88896)

10     ((typ? 1 or typ? I or typ?1 or typ?I) adj diabet$).ti,ab. (34800)

11     ((keto?resist$ or non?keto$) adj3 diabet$).ti,ab. (195)

12     (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).ti,ab. (3718)

13     or/1-12 (181975)

14     Dose-Response Relationship, Drug/ (353106)

15     Drug Administration Schedule/ (88851)

16     exp Drug Substitution/mt [Methods] (101)

17     ((down or drug or dose) adj3 titrat$).ti,ab. (3492)

18     ((drug or dose) adj3 reduc$).ti,ab. (43482)

19     ((drug or dose) adj3 de$escalation).ti,ab. (22)

20     ((drug or dose) adj3 taper$).ti,ab. (880)

21     discontinu$.ti. (7308)

22     withdraw$.ti. (18194)

23     spac$.ti. (43389)

24     (ceas$ or cessation).ti,ab. (74574)

25     stop$.ti. (11370)

26     (interval adj3 widening).ti,ab. (42)

27     (deprescri$ or de-prescri$).ti,ab. (67)

28     (interval adj3 spacing).ti,ab. (41)

29     discontinu$.ti. (7308)

30     eliminat$.ti. (23103)

31     reduc$.ti. (233877)

32     or/14-31 (848120)

33     Hypoglycemic Agents/ad, ae, tu, th, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Therapy, Toxicity] (33891)

34     (antihyperglycemic or anti-hypergylcemic).ti,ab. (1749)

35     Metformin/ad, tu [Administration & Dosage, Therapeutic Use] (5852)

36     Sulfonylurea Compounds/ad, tu [Administration & Dosage, Therapeutic Use] (2931)

37     (Meglitinides or Sulfonylurea).ti,ab. (4595)

38     Glyburide/ (5741)

39     glyburide$.ti,ab. (1363)

40     Thiazolidinediones/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (4497)

41     (Glitazones or TZD\*).ti,ab. (1913)

42     Dipeptidyl-Peptidase IV Inhibitors/ (2006)

43     Glucagon-Like Peptide 1/ (5407)

44     Insulin/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (32791)

45     Insulin, Long-Acting/ or Insulin, Short-Acting/ (2506)

46     or/33-45 (72670)

47     13 and 32 and 46 (4671)

48     limit 47 to (humans and "all adult (18 plus years)") (2666)

**Database: Embase Classic+Embase <1947 to 2015 July 10> OVID**

**Search Strategy:**

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1     exp diabetes mellitus/dm, an, dr, dt, to [Disease Management, Drug Analysis, Drug Resistance, Drug Therapy, Drug Toxicity] (108898)

2     \*insulin resistance/ (26542)

3     glucose intolerance/ (12779)

4     (impaired glucos$ toleranc$ or glucos$ intoleranc$ or insulin resistan$).ti,ab. (96560)

5     (MODY or NIDDM or T2DM).ti,ab. (25126)

6     (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or noninsulin?depend$).ti,ab. (13727)

7     (insulin$ depend$ or insulin$ depend$ or insulin?depend$ or insulin?depend$).ti,ab. (32969)

8     ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet$).ti,ab. (133858)

9     ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet$).ti,ab. (133858)

10     ((keto?resist$ or non?keto$) adj6 diabet$).ti,ab. (380)

11     (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).ti,ab. (5384)

12     or/1-11 (314677)

13     dose response/ (343849)

14     drug administration/ (53237)

15     drug substitution/ (26828)

16     (down adj3 titrat$).ti,ab. (315)

17     (dose adj3 titrat).ti,ab. (0)

18     (dose adj3 reduc$).ti,ab. (49933)

19     (dose adj3 de-escalation).ti,ab. (232)

20     (drug adj3 taper$).ti,ab. (185)

21     (dose adj3 taper$).ti,ab. (1244)

22     discontinu$.ti,ab. (142881)

23     withdraw$.ti,ab. (138218)

24     withdraw$.ti,ab. (138218)

25     spac$.ti,ab. (344087)

26     (ceas$ or cessation).ti,ab. (101336)

27     stop$.ti,ab. (146272)

28     (interval adj3 widening).ti,ab. (59)

29     (deprescri$ or de-prescri$).ti,ab. (95)

30     discontinu$.ti,ab. (142881)

31     eliminat$.ti,ab. (331425)

32     taper.ti,ab. (4448)

33     (reduce or reduction).ti,ab. (1486646)

34     or/13-33 (2880505)

35     12 and 34 (55064)

36     exp animals/ not humans.sh. (21045706)

37     35 not 36 (3457)

38     limit 37 to exclude medline journals (274)

**Appendix 2.** Risk of Bias Profile – Aspinall et al., 2011

|  |  |  |
| --- | --- | --- |
| **Domain** | **Assessment** | **Comment** |
| Bias due to confounding | Moderate risk | Possible confounding due to insufficient matching of intervention with control group (control group likely healthier at baseline), adjusted for using multivariable model |
| Bias in selection of participants into the study | Moderate risk | Selection bias likely since those in control group did not meet eligibilty criteria at baseline, and likely healthier at index date (less likely to experience hypoglycemia, less likely to have medication adjustment), adjusted for selection bias with model |
| Bias in measurement of interventions | Low risk | Intervention status is well defined and information collected at time of intervention |
| Bias due to departures from intended interventions | Critical risk | Contamination very likely and not adjusted for |
| Bias due to missing data | Low risk | Outcome data appears to be complete |
| Bias in measurement of outcomes | Moderate risk | Objective measures (A1C, discontinuation rate) unlikely to be affected by knowledge of intervention; hypoglycemia reporting may be affected, no information about pharmacy reporting errors |
| Bias in selection of the reported results | Low risk | No evidence of selective outcome reporting observed |
| Overall | Serious | Serious due to contamination of intervention in control group, which is likely to bias effects |

**Appendix 3.** Risk of Bias Profile – Sjoblom et al., 2008

|  |  |  |
| --- | --- | --- |
| **Domain** | **Assessment** | **Comment** |
| Bias due to confounding | Serious risk | Potential confounding, which was not adjusted for |
| Bias in selection of participants into the study | Serious risk | Selection into study related to intervention and outcome |
| Bias in measurement of interventions | Low risk | Intervention status unlikely to be influenced by knowledge of outcome |
| Bias due to departures from intended interventions | Moderate risk | Co-interventions not described |
| Bias due to missing data | Low risk | Follow-up data reasonably complete for A1C data and complete for mortality |
| Bias in measurement of outcomes | Low risk | Objective outcomes, unlikely to be influenced by knowledge of intervention |
| Bias in selection of the reported results | Low risk | No evidence of selective outcome reporting observed |
| Overall | Serious | Serious risk of bias due to selection bias, potential confounding |

**Appendix 4.** Summary of findings table – Aspinall et al., 2011

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Deprescribing of glyburide compared to usual care for Type 2 Diabetes** | | | | | | |
| **Patient or population:** Type 2 Diabetes, >65 y.o. **Settings:** Community dwelling  **Intervention:** Deprescribing of Glyburide **Comparison:** Control | | | | | | |
| **Outcomes** | **Illustrative comparative risks\* (95% CI)** | | **Relative effect (95% CI)** | **No of Participants (studies)** | **Quality of the evidence (GRADE)** | **Comments** |
| Assumed risk | Corresponding risk |
|  | **Control** | **Deprescribing of Glyburide** |  |  |  |  |
| **Change in A1C**  Follow-up: 3-9 months | Continuation of glyburide | The mean change in A1C in the intervention groups was **0.02 lower** (0.16 lower to 0.12 higher) |  | 3369 (1 study) | ⊕⊝⊝⊝ **very low**1,2,3 |  |
| **Hypoglycemia** ICD-9 Codes in health administrative databases and EMR Follow-up: mean 9 months | **26 per 1000**4 | **28 per 1000** (20 to 39) | **RR 1.08**  (0.78 to 1.5) | 6254 (1 study) | ⊕⊝⊝⊝ **very low**1,5,6 |  |
| **Discontinuation rate** No new prescription for glyburide Follow-up: mean 135 days | **560 per 1000**4 | **717 per 1000** (684 to 745) | **RR 1.28**  (1.22 to 1.33) | 6254 (1 study) | ⊕⊝⊝⊝ **very low**1 |  |
| \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; **RR:** Risk ratio; | | | | | | |
| GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate. | | | | | | |
| 1 Serious risk of bias due to contamination of intervention in control group 2 95% CI narrow  3 Mean difference very small at 0.02% 4 Usual care 5 95% CI around the estimate of effect includes both no effect and appreciable harm 6 Total number of events <300 | | | | | | |

**Appendix 5.**  Summary of findings – Sjoblom et al., 2008

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Deprescribing versus continuation of antihyperglycemics for type 2 diabetes in the frail elderly** | | | | | | |
| **Patient or population:** type 2 diabetes, frail elderly **Settings:** Nursing homes in Sweden **Intervention:** Deprescribing of antihyperglycemics **Comparison:** Continuation of antihyperglycemics | | | | | | |
| **Outcomes** | **Illustrative comparative risks\* (95% CI)** | | **Relative effect (95% CI)** | **No of Participants (studies)** | **Quality of the evidence (GRADE)** | **Comments** |
| Assumed risk | Corresponding risk |
|  | **Continuation of antihyperglycemics** | **Deprescribing of antihyperglycemics** |  |  |  |  |
| **Change in A1C** Follow-up: median 6 months |  | The mean change in A1C in the intervention groups was **1.1% higher** (0.56 lower to 1.64 higher) |  | 79 (1 study) | ⊕⊝⊝⊝ **very low**1,2 |  |
| **All-cause mortality** | **212 per 1000** | **157 per 1000** (62 to 397) | **RR 0.74**  (0.29 to 1.87) | 98 (1 study) | ⊕⊝⊝⊝ **very low**1,3 |  |
| \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; **RR:** Risk ratio; | | | | | | |
| GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate. | | | | | | |
| 1 Very serious risk of bias due to selection bias and potential confounding 2 95% CI wide, <400 participants 3 95% CI wide, number of events <300 | | | | | | |