BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"In obese or overweight (BMI > 25 kg/m2) adults without type two diabetes, how effective is Metformin combined with exercise and a controlled diet, compared to exercise and a controlled diet alone, improving weight related outcomes (e.g. BMI, blood pressure, blood cholesterol, HbA1c)?"

Clarification of question using PICO structure

Patients: Obese or overweight (BMI > 25 kg/m2) adults who do not have type two diabetes
Intervention: Metformin combined with exercise and a controlled diet
Comparator: Exercise and a controlled diet alone
Outcome: Weight related outcomes (e.g. BMI, blood pressure, blood cholesterol, HbA1c)

Clinical and research implications

Overall, the evidence on the effectiveness of adding metformin treatment to lifestyle interventions (exercise and diet) was contradictory and limited to specific population. There was evidence that additional metformin treatment was ineffective in women with polycystic ovary syndrome, but may have some small benefits for people with chronic schizophrenia. Further high quality RCTs and/or appropriate meta-analyses are needed to confirm these findings and to assess the effectiveness of adding metformin treatment to lifestyle interventions in other populations.

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What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two systematic reviews,[1,2] and one additional RCT,[3] which reported data relevant to this evidence summary. One systematic review included randomised controlled trials (RCTs) which compared insulin sensitising drugs, alone or in combination with lifestyle interventions, to placebo, alone or in combination with lifestyle interventions.[1] All but two of the studies included in this review were conducted in women with polycystic ovary syndrome (PCOS).[1] For this review, a subgroup analysis of five RCTs which included studies comparing high dose metformin (>1,500 mg/d)+ diet to placebo + diet was included in the evidence summary, as this analysis was considered to provide data matching the PICO criteria.[1] The second systematic review included 31 RCTs conducted in a variety of adult populations at risk of developing diabetes mellitus.[2] This review included 13 studies which applied lifestyle interventions in all participants, but these studies were not analysed separately; the results of this review are therefore of limited applicability to this evidence summary.[2] The additional RCT was conducted in overweight adults with chronic schizophrenia or schizoaffective disorder and compared metformin to placebo, where all participants also received a lifestyle intervention.[3]

Main Findings

The sub-group analysis form the first systematic review found no statistically significant benefit, in terms of BMI reduction, for adding metformin treatment to lifestyle interventions, WMD -0.84 (95% CI: -2.20 to 0.51).[1] The second systematic review found that metformin treatment was associated with a reduction in the incidence of new-onset diabetes, greater reductions in BMI and improvements in lipid profile and insulin resistance, compared to placebo.[2] However, this review did not consider the additive effects of metformin over exercise and controlled diet.[2] The additional RCT found that metformin treatment was associated with small but statistically significant decreases (from baseline to 16 weeks) in weight, BMI, triglycerides, and HbA_{1c}, compared to placebo, where all participants also received a lifestyle intervention; the mean between group differences were -2.0 (95% CI: -3.4 to -0.6), -0.7 (95% CI: -1.1 to -0.2), -20.2 (95% CI: -39.2 to -1.3) and -0.07 (95% CI: -0.14 to -0.004), respectively.[3]

Authors Conclusions

One systematic review concluded that a structured lifestyle modification programme to achieve weight loss should still be the first line treatment in obese women with or without PCOS. A second systematic review found that metformin treatment in persons at risk for diabetes improves weight, lipid profiles, and insulin resistance, and reduces new-onset diabetes by 40%. One additional RCT, conducted in clinically stable, overweight adult patients with chronic schizophrenia or schizoaffective disorder, found that metformin was moderately effective in reducing weight and some other risk factors for cardiovascular disease.

Reliability of conclusions/Strength of evidence

One generally well conducted systematic review, with some weaknesses in the synthesis methods, found no significant difference in change in BMI between metformin + a lifestyle intervention and placebo + a lifestyle intervention.[1] This finding is likely to be reliable, but it should be noted that included studies were mainly conducted in women with PCOS and findings may not be generalisable to other populations.[1] A second generally well conducted systematic review, also with some weaknesses in the synthesis methods, found that metformin treatment was associated with a reduction in the incidence of new-onset diabetes, and improvements in BMI, profile and insulin

resistance, compared to placebo.[2] The main analytical weakness in this review entailed the pooling of studies with different intervention and control arms (with and without lifestyle co-interventions); for this reason results may be unreliable and are of limited applicability to this evidence summary (PICO criteria not met).[2] Finally, one additional high quality RCT, conducted in patients with schizophrenia or schizoaffective disorder, found that metformin treatment was associated with small, but statistically significant, decreases in weight, BMI, triglycerides, and HbA_{1c}, compared to placebo, where all participants also received a lifestyle intervention.[3] These results are likely to be reliable for this population, but may not be generalisable to other populations; in particular, it should be noted that >75% of participants in this study were receiving one or more anti-psychotic agents, causing weight gain.[3]

What do guidelines say?

For individuals at risk of type two diabetes, NICE recommends the following;
(CG38 pp.37)

- Use clinical judgement on whether (and when) to offer standard-release metformin to support lifestyle change for people whose HbA1c or fasting plasma glucose blood test results have deteriorated if:
    - this has happened despite their participation in an intensive lifestyle-change programme, or
    - they are unable to participate in an intensive lifestyle-change programme.
- Discuss with the person the potential benefits and limitations of taking metformin, taking into account their risk and the amount of effort needed to change their lifestyle to reduce that risk. Explain that long-term lifestyle change can be more effective than drugs in preventing or delaying type 2 diabetes.
- Continue to offer advice on diet and physical activity along with support to achieve their lifestyle and weight-loss goals.
- Start with a low dose (for example, 500 mg once daily) and then increase gradually as tolerated, to 1500–2000 mg daily. If the person is intolerant of standard metformin consider using modified-release metformin.
- Prescribe metformin for 6–12 months initially. Monitor the person's fasting plasma glucose or HbA1c levels at 3-month intervals and stop the drug if no effect is seen.

For individuals with schizophrenia SIGN guidelines state the following;
(CG 131, pp. 12)

- Metformin is not licensed for the control of weight gain in individuals taking antipsychotic medications.
- Metformin should be considered for service users who are experiencing weight gain on antipsychotic medications.

The evidence included in this summary is consistent with current guidelines.

Date question received: 18/12/2013
Date searches conducted: 02/01/2014
Date answer completed: 20/01/2014

References

SRs

1. Nieuwenhuis-Ruifrok, A.E., Kuchenbecker, W.K.H., Hoek, A., Middleton, P. and Norman, R.J. (2009) Insulin sensitizing drugs for weight loss in women of reproductive age who are overweight or obese: systematic review and meta-analysis. *Human Reproductive Update 15* (**1**) pp. 57-68.

2. Salpeter, S.R., Buckley, N.S., Kahn, J.A. and Salpeter, E.E. (2008) Meta-analysis: Metformin Treatment in Persons at Risk for Diabetes Mellitus. *The American Journal of Medicine 121* (**2**) pp. 149-157.

RCTs

3. Jarskog, L.F., Hamer, R.M., Catellier, D.J., Stewart, D.D., LaVange, L., Ray, N., Golden, L.H., Lieberman, J.A. and Stroup, T.S. (2013)Metformin for Weight Loss and Metabolic Control in Overweight Outpatients With Schizophrenia and Schizoaffective Disorder. *American Journal of Psychiatry 170* pp. 1032-1040.

Guidelines

National Institute for Health and Care Excellence (2012) Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. CG38. London: National Institute for Health and Care Excellence

Scottish Intercollegiate Guidelines Network (2013) Management of Schizophrenia. A National Clinical Guideline. CG131. Edinburgh: Scottish Intercollegiate Guidelines Network.

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Nieuwenhuis-Ruifrok et al. (2009)	08/2007	*Participants:* Overweight (BMI 25-29.9kg/m²)or obese (BMI ≥ 30 kg/m²) women of reproductive age, *Intervention*: Insulin sensitising drugs: metformin, pioglitazone, rosiglitazone or d-chiro-inositol, alone or in combination with diet advice and/or a lifestyle modification programme. *Comparator:* One or more of the following: placebo only or placebo with diet advice and/or a lifestyle modification programme. *Outcome:* BMI. *Study design:* RCTs	n = 14 studies, 649 participants	The objective of this systematic review was to assess whether treatment of women, of reproductive age who are overweight or obese, with insulin sensitising agents contributes to weight loss in comparison to placebo and diet and/or a lifestyle modification programme. One sub-group analysis, which included five trials with a total of 247 participants, was directly relevant to this evidence summary. This sub-group analysis included studies which compared high dose metformin (>1,500 mg/d)+ diet to placebo + diet. Study durations ranged from 4 to 6 months. All study participants had a diagnosis of PCOS and/or hirsuitism. The summary estimate derived from these five studies found no statistically significant difference in the change in BMI (baseline to end of study) between the two treatment groups (metfromin + diet versus placebo + diet), i.e. metformin appeared to offer no	The review included a clearly stated research objective, but and inclusion criteria were partially defined. Three bibliographic databases were searched for relevant studies and searches were supplemented by hand searching, reference screening and contact with study authors. The study selection process included measures to minimise error and/or bias

				significant additional benefit over dietary changes alone: WMD -0.84 (95% CI: -2.20 to 0.51). When high dose metformin without diet was compared to placebo without diet a small, but statistically significant, treatment effect was seen.	(involvement of two or more reviewers), but it was not clear whether the same methods were applied to data extraction and quality assessment. The methodological quality of included studies was assessed based on selection bias, attrition bias, performance bias, and detection bias. Studies were combined using random effects meta-analyses and appropriate sub-groups. However, women who did not complete the included trials were excluded form analyses. In

					addition, subgroups appeared to include more than one variable of interest, e.g. all but one of the >8 weeks duration metformin subgroup were studies with diet as a co-intervention, making it unclear whether diet or duration of intervention was driving the observed treatment effect.
Salpeter et al. (2008)	11/2006	*Participants:* People without diabetes, considered to be at risk of developing diabetes. Studies evaluating evaluating lipodystrophy associated with human immunodeficiency virus infection were excluded. *Intervention:* Metformin alone or in combination with lifestyle measures such as diet and exercise *Comparator:* Placebo or no treatment alone or in	N = 31 studies, 4,590 participants	The objective of this systematic review was to assess the effects of metformin treatment on metabolic parameters and new-onset diabetes, in people at risk of developing diabetes. The mean age of study participants was 45.7 ± 9.5 years, and the mean baseline BMI was 32.3 ± 4.0. The mean metformin dose, across studies included in the review, was 1,600 mg/g (range 500 to 2,550 mg/d), and the	The review included a clearly stated research objective and defined appropriate inclusion criteria. Three bibliographic databases were searched (without

		combination with lifestyle measures. *Outcomes:* Metabolic change parameters (BMI, lipids and insulin resistance) and incidence of new onset of diabetes. *Study design:* RCTs of at least 8 weeks duration.		mean study duration was 1.8 years (range 0.15 to 3 years). The overall dropout rates were similar for the treatment (27.4%) and control (24.9%) groups. Thirteen of the included studies applied lifestyle modification or diet interventions in all participants, but no separate sub-group analyses were conducted to assess the possible effects of co-interventions (or other variables). Treatment with metformin was associated with a significant reduction in the incidence of new onset diabetes compared with placebo or no treatment: OR 0.6 (95% CI: 0.5 to 0.8), 6 studies. Treatment with metformin was associated with a significantly greater reduction in BMI than placebo or no treatment: WMD -5.3% (95% CI: -6.7% to -3.5%), 18 studies. Metformin treatment increased high-density lipoprotein (HDL) cholesterol (WMD 5.0% (95% CI: 1.6% to 8.3%), 15 studies) and reduced low density lipoprotein (LDL) cholesterol (WMD -5.6% (95% CI -8.3% to -3.0%), 13 studies), LDL/HDL ratio (WMD -8.5% (95% CI: -14.0% to -2.6%), 13 studies), and triglycerides (WMD -5.3% (95% CI: -	language restriction) for relevant studies and searches were supplemented by hand searching, reference screening and contact with study authors. The data extraction process included measures to minimise error and/or bias (two reviewers involved), but it was unclear whether similar measures were applied to study selection and quality assessment. The methodological quality of included studies was assessed using criteria corresponding to

				10.5% to -0.03%), 19 studies) compared with placebo or no treatment. Treatment with metformin was associated with a significant reduction in insulin resistance compared to placebo or no treatment: WMD -22.6 (95% CI: -27.3 to -18.0), 24 studies.	the Cochrane risk of bias tool. Overall, summary estimates were calculated using a fixed effect model and no sub-group analyses were included (e.g. for studies which included diet or lifestyle co-interventions)

RCTs

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
Jarskog et al. (2013)	*Participants:* Overweight (BMI ≥27), clinically stable, adult, outpatients with chronic schizophrenia or schizoaffective disorder (DSM-IV) with a duration of illness ≥1 year. Concomitant medications were allowed if dosages were unchanged for 1 month prior to entry. Exclusion criteria: Clinical Global Impressions Severity scale rating ≥6;	n = 148.	The objective of this study was to assess the effectiveness of metformin, in addition to lifestyle interventions, for promoting weight loss in overweight outpatients with chronic schizophrenia or schizoaffective disorder. All participants received weekly diet and exercise counselling during the study. The intervention was adapted from a weight reduction program developed for patients with severe mental illnesses and included eight 20- to 30-minute lessons and seven interim telephone calls to reinforce lessons.	Randomisation used a central-computerised system. No details of allocation concealment were reported.

	diabetes mellitus; fasting glucose level >125 mg/dL; current or previous treatment with metformin; current treatment with insulin or an oral hypoglycemic; treatment with more than two antipsychotics; use of any prescription or non-prescription medication for weight loss within the past month; pregnancy or breastfeeding; uncorrected thyroid disorder; any serious or unstable medical condition. *Intervention:* Metformin, taken for 16 weeks, tirated up to 1,000 mg/d, as tolerated (maximum daily dose 2,000 mg, plus weekly diet and exercise counselling. *Comparator:* Placebo plus weekly diet and exercise counselling. *Outcomes:* Change in body weight from baseline to week 16. Secondary outcome measures included change from baseline to week 16 in BMI, waist circumference, waist-hip ratio, levels of fasting total cholesterol, non-highdensity lipoprotein (non-HDL) cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, insulin, and hemoglobin A1c (HbA1c).		The mean age of study participants was 43.2 ± 11.06 years and 55% were male. 77.8% of participants were using one or more anti-psychotic agents, causing weight gain. The mean weight of study participants at baseline was 101.9 ± 18.5 kg, and the mean BMI was 34.6 ± 5.9. The mean baseline fasting plasma glucose was 97.0 ± 9.7 mg/dL and the mean baseline HbA_{1c} was 5.5% ± 0.4%. Baseline lipids were also reported. Adherence to study medication was similar in the metformin (94.9%) and placebo (96.0%) groups, and adherence to the behavioural intervention was also similar (84.9% in the metformin group and 89.7% in the placebo group). Metformin treatment was associated with statistically significantly greater decreases (from baseline to 16 weeks) in weight, BMI, triglycerides, and HbA_{1c}, compared to placebo; the mean between group differences were -2.0 (95% CI: -3.4 to -0.6), -0.7 (95% CI: -1.1 to -0.2), -20.2 (95% CI: -39.2 to -1.3) and -0.07 (95% CI: -0.14 to -0.004), respectively. All other outcome measures were non-significant.	The study was reported as 'double blind' and blinding was described with respect to participants and treating clinicians, but it was unclear whether outcome assessors were blind to treatment groups. Efficacy was assessed using a modified intention-to-treat approach (participants who received at least one dose of study medication and had at least one post-baseline

				weight measure were included in the analyses) Results were reported for all specified outcomes measures.

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Nieuwenhuis-Ruifrok et al. (2009)	☺	☺	?	☺	☹
Salpeter et al. (2008)	☺	☺	?	☺	☹

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Jarskog et al. (2013)	☺	?	☺	?	☺	☺

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	metformin AND weight	25	2
DARE	(metformin) IN DARE 200 2 (dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance) IN DARE 0 3 MeSH DESCRIPTOR Metformin EXPLODE ALL TREES 151 4 #1 OR #2 OR #3 255 5 (obes*) IN DARE 739 6 ((over ADJ2 weight) OR overweight) IN DARE 314 7 (adipos*) IN DARE 55 8 MeSH DESCRIPTOR Obesity EXPLODE ALL TREES 766 9 MeSH DESCRIPTOR Obesity, Morbid EXPLODE ALL TREES 172 10 MeSH DESCRIPTOR Overweight EXPLODE ALL TREES 782 11 #5 OR #6 OR #7 OR #8 OR #9 OR #10 1147 12 #4 AND #11	59	2
Primary studies			
CENTRAL	#1 MeSH descriptor: [Obesity] explode all trees 6833 #2Enter terms for searcobese6476 #3Enter terms for searcoverweight3947 #4Enter terms for searc"weight controlled"26 #5Enter terms for searc#1 or #2 or #3 or #410620 #6Enter terms for searcmetformin2321 #7Enter terms for searcdiet or exercise60236 #8Enter terms for searc#6 and #7527 #9Enter terms for searc#5 and #8226 #10Enter terms for searcmetformin not diabetes680	41	

	#11Enter terms for searc#10 and #770 #12Enter terms for searc#11 and #5 41		
PsycINFO	53. PsycINFO; OBESITY/; 14660 results. 54. PsycINFO; obese.ti,ab; 9449 results. 55. PsycINFO; overweight.ti,ab; 8385 results. 56. PsycINFO; 53 OR 54 OR 55; 20101 results. 57. PsycINFO; METFORMIN/; 0 results. 58. PsycINFO; metformin.ti,ab; 196 results. 59. PsycINFO; 57 OR 58; 196 results. 60. PsycINFO; DIET/; 0 results. 61. PsycINFO; EXERCISE/; 14065 results. 62. PsycINFO; 60 OR 61; 14065 results. 63. PsycINFO; 59 AND 62; 4 results. 64. PsycINFO; 56 AND 63; 1 results. 65. PsycINFO; DIABETES MELLITUS/; 3611 results. 66. PsycINFO; 59 not 65; 171 results. 67. PsycINFO; 62 AND 66; 3 results. 68. PsycINFO; 56 AND 67; 1 results. 69. PsycINFO; 68 AND 46; 0 results. 70. PsycINFO; exp DIABETES MELLITUS/; 3611 results. 71. PsycINFO; 59 not 70; 171 results. 72. PsycINFO; 62 AND 71; 3 results. 73. PsycINFO; 56 AND 72; 1 results. 74. PsycINFO; 46 AND 73; 0 results. 75. PsycINFO; EATING BEHAVIOR [+NT]/ OR NUTRITION/ OR WEIGHT CONTROL/; 16122 results. 76. PsycINFO; 61 OR 75; 29362 results. 77. PsycINFO; diet.ti,ab; 15154 results. 78. PsycINFO; 76 OR 77; 41636 results. 79. PsycINFO; 58 AND 78; 33 results.	18	

	80. PsycINFO; 56 AND 79; 18 results.		
Embase	17. EMBASE; OBESITY/; 238907 results. 18. EMBASE; obese.ti,ab; 102089 results. 19. EMBASE; overweight.ti,ab; 50489 results. 20. EMBASE; 17 OR 18 OR 19; 271839 results. 21. EMBASE; METFORMIN/; 31879 results. 22. EMBASE; metformin.ti,ab; 14309 results. 23. EMBASE; 21 OR 22; 32898 results. 24. EMBASE; DIET/; 139053 results. 25. EMBASE; EXERCISE/; 174429 results. 26. EMBASE; 24 OR 25; 303943 results. 27. EMBASE; 23 AND 26; 2871 results. 28. EMBASE; 20 AND 27; 1199 results. 29. EMBASE; DIABETES MELLITUS/; 329099 results. 30. EMBASE; 23 not 29; 23835 results. 31. EMBASE; 26 AND 30; 1912 results. 32. EMBASE; 20 AND 31; 808 results. 33. EMBASE; random*.ti,ab; 869651 results. 34. EMBASE; factorial*.ti,ab; 22435 results. 35. EMBASE; (crossover* OR cross-over*).ti,ab; 69159 results. 36. EMBASE; placebo*.ti,ab; 199410 results. 37. EMBASE; (doubl* ADJ blind*).ti,ab; 142963 results. 38. EMBASE; (singl* ADJ blind*).ti,ab; 14261 results. 39. EMBASE; assign*.ti,ab; 236791 results. 40. EMBASE; allocat*.ti,ab; 81853 results. 41. EMBASE; volunteer*.ti,ab; 176368 results. 42. EMBASE; CROSSOVER PROCEDURE/; 39341 results. 43. EMBASE; DOUBLE BLIND PROCEDURE/; 119415 results. 44. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 362850 results. 45. EMBASE; SINGLE BLIND PROCEDURE/; 18704 results.	43	

	46. EMBASE; 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45; 1402658 results. 47. EMBASE; 32 AND 46; 126 results. 48. EMBASE; exp DIABETES MELLITUS/; 574955 results. 49. EMBASE; 23 not 48; 8907 results. 50. EMBASE; 26 AND 49; 481 results. 51. EMBASE; 20 AND 50; 224 results. 52. EMBASE; 46 AND 51; 43 results.		
Medline	1. MEDLINE; OBESITY/; 130659 results. 2. MEDLINE; obese.ti,ab; 80255 results. 3. MEDLINE; overweight.ti,ab; 39493 results. 4. MEDLINE; 1 OR 2 OR 3; 174300 results. 5. MEDLINE; METFORMIN/; 7396 results. 6. MEDLINE; metformin.ti,ab; 9575 results. 7. MEDLINE; 5 OR 6; 10927 results. 8. MEDLINE; DIET/; 110990 results. 9. MEDLINE; EXERCISE/; 71198 results. 10. MEDLINE; 8 OR 9; 177054 results. 11. MEDLINE; 7 AND 10; 304 results. 12. MEDLINE; 4 AND 11; 95 results. 13. MEDLINE; DIABETES MELLITUS/; 92383 results. 14. MEDLINE; 7 not 13; 10039 results. 15. MEDLINE; 10 AND 14; 255 results. 16. MEDLINE; 4 AND 15; 74 results. 17. MEDLINE; "randomized controlled trial".pt; 395884 results. 18. MEDLINE; "controlled clinical trial".pt; 90603 results. 19. MEDLINE; randomized.ab; 311360 results. 20. MEDLINE; placebo.ab; 166092 results. 21. MEDLINE; "drug therapy".fs; 1786844 results. 22. MEDLINE; randomly.ab; 220035 results. 23. MEDLINE; trial.ab; 328153 results. 24. MEDLINE; groups.ab; 1394874 results.	55	

	25. MEDLINE; 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24; 3474597 results. 26. MEDLINE; 16 AND 25; 55 results.		
Summary	**NA**	**NA**	

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