NICE advice

Polycystic ovary syndrome: metformin in women not planning pregnancy

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in February 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Metformin is licensed in the UK for the control of blood glucose in people with type 2 diabetes. It has also been used to treat polycystic ovary syndrome (PCOS). Metformin is not licensed in the UK for this indication so its use in PCOS is off-label.

This evidence summary relates to metformin for PCOS in women who are not planning pregnancy. The use of metformin for treating infertility in women with PCOS is not covered by this evidence summary.

Five small randomised controlled trials (RCTs) included in a Cochrane systematic review, and 4 RCTs published after the Cochrane review, provide the evidence for this summary.

There is no good evidence that regimens containing metformin are statistically significantly different from co-cyprindiol in controlling hirsutism in women with PCOS. Two small studies found no statistically significant difference between metformin and co-cyprindiol in effects on acne but the assessment methods were unclear. Metformin was less effective at improving menstrual regularity than co-cyprindiol. There was no or insufficient data in the studies included in this evidence summary from which to draw conclusions on the effectiveness of metformin for long-

term outcomes such as preventing type 2 diabetes, cardiovascular events or endometrial cancer in women with PCOS.

Metformin use is associated with gastrointestinal adverse effects (nausea, vomiting and diarrhoea), which can be severe. The Cochrane review found that metformin caused a significantly higher incidence of gastrointestinal adverse effects that were severe (leading to treatment discontinuation) compared with co-cyprindiol, and a significantly lower incidence of other severe adverse effects (weight gain, high blood pressure, depression, chest pain and headache). Among all 9 trials there was significant heterogeneity in the rates of treatment discontinuation, which was not always because of adverse effects.

The annual cost of metformin at 1.5–2 g per day ranges from £30.03 to £83.20, depending on whether standard or modified-release tablets are prescribed.

Alternative commonly used treatments for hirsutism, acne and menstrual irregularity in PCOS in women not planning pregnancy are:

- Co-cyprindiol, a combination product containing cyproterone and ethinylestradiol. Co-cyprindiol is licensed for treating severe acne refractory to prolonged oral antibiotic therapy, and moderately severe hirsutism. It is not licensed specifically for use in PCOS.
- The combined oral contraceptive pill. This is not licensed for controlling menstrual irregularity in PCOS.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Metformin is commonly used for controlling blood glucose in people with diabetes. It reduces glucose production in the liver and improves the insulin sensitivity of other cells. Many women with polycystic ovary syndrome (PCOS) have insulin resistance so metformin has also been used to treat PCOS.

Regulatory status of metformin

Metformin is not licensed in the UK for treating PCOS and so its use for PCOS is off-label. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using metformin outside its authorised indications.

Metformin is licensed for the treatment of type 2 diabetes mellitus, particularly in people who are overweight, when dietary management and exercise alone do not result in adequate glycaemic control.

Evidence statements

Five small randomised controlled trials (RCTs) included in a Cochrane systematic review, and 4 RCTs published after the Cochrane review, provide the evidence for this summary. The usual comparator treatment was co-cyprindiol (ethinylestradiol 35 micrograms plus cyproterone 2 mg) alone. A small number of studies assessed metformin versus metformin plus cyprindiol. No RCTs compared metformin with placebo. Only outcomes that are directly relevant to patients (and not surrogate outcomes such as biochemical markers) are discussed in this evidence summary.

- There was conflicting evidence regarding the effects of metformin on hirsutism compared with co-cyprindiol. Four RCTs found no statistically significant difference between metformin monotherapy and co-cyprindiol monotherapy on hirsutism. One RCT found that metformin monotherapy was statistically significantly more effective than co-cyprindiol monotherapy. One RCT found no statistically significant difference between co-cyprindiol plus metformin and co-cyprindiol monotherapy. Results from 2 other RCTs suggest that co-cyprindiol or co-cyprindiol plus metformin were superior to metformin monotherapy, but they are not clearly reported.
- Two small studies found no statistically significant difference between metformin and co-cyprindiol on acne but the assessment methods used were not reported.

- Metformin monotherapy was less effective at improving menstrual regularity compared with co-cyprindiol monotherapy in 2 RCTs and not statistically significantly different in 2 other RCTs. In 2 further RCTs, metformin monotherapy was observed to be less effective than co-cyprindiol monotherapy (both RCTs) or metformin plus co-cyprindiol (1 of the RCTs) but statistical analysis was not performed.
- There was no or insufficient data in the studies included in this evidence summary from which to draw conclusions on the effectiveness of metformin for long-term outcomes such as preventing type 2 diabetes, cardiovascular events or endometrial cancer in women with PCOS.
- Gastrointestinal adverse effects, which occasionally caused women to stop treatment, were more commonly reported with metformin than co-cyprindiol. Other adverse effects that caused women to stop treatment (weight gain, high blood pressure, depression, chest pain and headache) were more commonly reported with co-cyprindiol than metformin.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the Evidence review section.

Of the total of 9 RCTS, no RCTs compared metformin, alone or in combination, with placebo. None of the RCTs was double blind. Three of the RCTs reported significant differences between baseline characteristics of the treatment and control groups despite randomisation. Allocation was concealed in 4 RCTs but allocation concealment was unclear or not stated in others. Only 2 RCTs conducted an intention-to-treat analysis (ITT; Elter et al. 2002 and Luque-Ramirez et al. 2007); the other RCTs analysed results only from those women who completed the trial (when the number of participants is given, this is the number of women analysed unless stated otherwise). All except 2 were open label (Elter et al. 2002 and Wu et al. 2008 were single blind). Withdrawal rates were up to 44%. The RCTs showed a significant degree of heterogeneity in terms of treatment duration, assessment methods and inclusion criteria. Only 1 trial was longer than 6 months and all were small (n=28–100).

Efficacy

Hirsutism

All RCTs which reported this outcome used the Ferriman–Gallwey score. Three RCTs (Morin-Papunen et al. 2000 and Morin-Papunen et al. 2003, combined n=35; Cetinkalp et al. 2009, n=80) found no statistically significant difference between metformin and co-cyprindiol. One study (Harborne et al. 2003, n=34) found a statistically significant reduction in hirsutism with metformin

compared with co-cyprindiol, measured using the Ferriman-Gallwey score and also by patient self-assessment. A fourth study (Luque-Ramirez et al. 2007) found no statistically significant differences between metformin and co-cyprindiol in an analysis based on the 27 women who completed the study, but a statistically significant difference in favour of co-cyprindiol based on an ITT analysis with last observation carried forward (n=34); this was the baseline observation in 5 women taking metformin and none of those taking co-cyprindiol.

Elter et al. (2002) (n=40) found no statistically significant difference in hirsutism score with metformin plus co-cyprindiol compared with co-cyprindiol alone. Meyer et al. (2007) (n=100) found no statistically significant difference between metformin, co-cyprindiol, and combination therapy with an oral contraceptive plus spironolactone. Wu et al. (2008) (n=60) found that hirsutism improved in women taking co-cyprindiol monotherapy and co-cyprindiol plus metformin but not in those taking metformin monotherapy (between-group statistical significance not reported).

Although reductions from baseline were statistically significant in most of the trials, mean absolute reductions on the 36-point Ferriman–Gallwey score were 2–3 points or less.

Acne

Harborne et al. (2003) (n=34) used a patient-self-assessed acne score and found no statistically significant difference in score between metformin and co-cyprindiol. Cetinkalp et al. (2009) (n=80) also found no statistically significant difference in acne from baseline or between metformin and co-cyprindiol, but the assessment methods used were not reported.

Menstrual regularity

Two RCTs (Morin-Papunen et al. 2000 and Morin-Papunen et al. 2003) (combined n=35) found metformin to be statistically significantly less effective than co-cyprindiol in improving menstrual regularity. Cetinkalp et al. (2009) (n=80) found no statistically significant difference between metformin and co-cyprindiol in effect on menstrual regularity and Meyer et al. (2007) (n=100) found no statistically significant difference between metformin, co-cyprindiol, and combination therapy with an oral contraceptive plus spironolactone. In the study by Luque-Ramirez et al. (2007), menstrual regularity was restored in 6 of the 12 women receiving metformin and in all 15 women receiving co-cyprindiol (p value not stated). Wu et al. (2008) (n=60) found that menstrual regularity was fully restored in all women receiving co-cyprindiol monotherapy and co-cyprindiol plus metformin, but in only approximately 28% of those receiving metformin monotherapy (p value not stated).

Other outcomes

Only 1 RCT reported on the development of type 2 diabetes in women with PCOS (Morin-Papunen et al. 2000). Data was available for 18 women over a 6-month period) and found no statistically significant difference between metformin and co-cyprindiol in the rates of type 2 diabetes. No RCTs included in this evidence summary reported the effects of metformin on the risk of cardiovascular events or endometrial cancer in women with PCOS.

Safety

Metformin is associated with gastrointestinal adverse effects (nausea, vomiting and diarrhoea), which can be severe. The Cochrane review (Costello et al. 2007) found that metformin caused a significantly higher incidence of gastrointestinal adverse effects that were severe (leading to treatment discontinuation) compared with co-cyprindiol, and a significantly lower incidence of other severe adverse effects (weight gain, high blood pressure, depression, chest pain and headache). Among all 9 trials there was significant heterogeneity in the rates of treatment discontinuation, which was not always because of adverse effects.

Cost effectiveness and cost

No studies on cost effectiveness were identified. The annual cost of metformin at a dose of 1.5–2 g per day ranges from £30.03 to £83.20, depending on whether standard or modified-release tablets are prescribed (costs taken from the Drug Tariff January 2012).

Relevance to NICE guidance programmes

Use of metformin for treating PCOS in women who are not planning pregnancy has not been assessed as part of a NICE technology appraisal work programme and is not currently listed as a proposed technology appraisal or an appraisal in development.

Fertility: assessment and treatment for people with fertility problems (NICE clinical guideline 156) recommends women with WHO Group II ovulation disorders or anovulatory infertility should be offered treatment including metformin in certain circumstances.

NICE guidance also exists for the licensed indications for metformin:

- Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults (NICE clinical guideline 15)

- Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87).
- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period (NICE clinical guideline 63).

NICE is currently updating its guidance on type 1 and type 2 diabetes in children and young people (expected June 2014), diabetes in pregnancy (expected June 2014), type 1 diabetes in adults (expected July 2014), and type 2 diabetes in adults (publication date to be confirmed).

Intervention and alternatives

Metformin reduces glucose production in the liver and improves the insulin sensitivity of other cells.

Condition

PCOS is characterised by irregular menstrual cycles, infertility, hirsutism and acne. It is the most common condition affecting the endocrine system among women (Costello et al. 2007). Women with PCOS have an increased risk of developing type 2 diabetes compared with women of similar age and weight, and are also thought to be at increased risk for endometrial cancer (Costello et al. 2007).

The exact cause of PCOS is unknown. Insulin resistance (reduced glucose response to a given amount of insulin) is present in 65–70% of all women with PCOS (Marshall and Dunaif 2012), with consequent compensatory hyperinsulinaemia. Hyperinsulinaemia directly stimulates both ovarian and adrenal androgen secretion and suppresses liver sex hormone-binding globulin synthesis, resulting in an increase in free, biologically active androgens. This causes premature follicular atresia and anovulation along with the other clinical manifestations of hyperandrogenism such as hirsutism and acne (Costello et al. 2007).

Alternative treatment options

No studies compared metformin to placebo. The most common comparator to metformin in the studies identified for this evidence summary was co-cyprindiol (ethinylestradiol 35 micrograms plus cyproterone 2 mg) alone. A small number of studies compared metformin with metformin plus co-cyprindiol. Although co-cyprindiol also acts as an oral contraceptive, the summary of product characteristics states that it is not indicated for women solely for contraception, but should be reserved for those women needing treatment for the androgen-dependent conditions for which it is indicated: severe acne and moderately severe hirsutism. Low-dose oral contraceptives can also

be prescribed to help regulate the menstrual cycle and are licensed for oral contraception but not for PCOS (British National Formulary, December 2012).

Other treatments for the symptoms of PCOS include weight loss, cholesterol-lowering medication and acne medication. Additional treatments are available for women with PCOS who are trying to conceive but these are outside the scope of this evidence summary.

Evidence review: efficacy

One Cochrane systematic review of 5 RCTs, and 4 RCTs published after the Cochrane review provide the evidence for this summary. Only outcomes that are directly relevant to patients (and not surrogate outcomes such as biochemical markers) are discussed in this evidence summary.

Cochrane review

The Cochrane review (Costello et al. 2007, assessed as up-to-date in 2006) included 5 RCTs (1 additional study discussed in the Cochrane review was based on data from 2 of these RCTs: it analysed only lipid levels as outcomes and is not discussed here). All women in the trial had PCOS but inclusion criteria varied between studies.

Three RCTs (Morin-Papunen et al. 2000, Morin-Papunen et al. 2003 and Harborne et al. 2003) compared metformin monotherapy with co-cyprindiol monotherapy. The dose of metformin was 500 mg 3 times a day in 1 of these RCTs (Harborne et al. 2003) and 500 mg twice a day for 3 months followed by 1000 mg twice a day for 3 months in the other 2 RCTs (Morin-Papunen et al. 2000 and Morin-Papunen et al. 2003).

Two RCTs investigated metformin in combination therapy. One RCT (Elter et al. 2002) compared metformin 500 mg 3 times a day plus co-cyprindiol with co-cyprindiol monotherapy. One RCT (Cibula et al. 2005) compared metformin 500 mg 3 times a day plus oral contraceptive with oral contraceptive monotherapy. The oral contraceptive used in this RCT contained ethinylestradiol 35 micrograms plus norgestimate 250 micrograms (available in the UK as Cilest).

Only 1 RCT (Elter et al. 2002) conducted an ITT analysis and this study was single blind (clinical outcome assessors were blind to the treatment allocation). The other RCTs were open label, and analyses included only those women who completed the trial: withdrawal rates ranged from 6.7% to 44%. Allocation concealment was assessed by the Cochrane reviewers as clear in all but 1 RCT; in that RCT (Elter et al. 2002), the random allocation sequence was generated by computer but the Cochrane reviewers assessed allocation concealment as unclear.

Hirsutism

All RCTs which reported this outcome used the Ferriman–Gallwey score. The Cochrane meta-analysis of two RCTs (Morin-Papunen et al. 2000 and Morin-Papunen et al. 2003, combined n=52, outcomes available for 35 women) found no statistically significant difference between metformin monotherapy and co-cyprindiol monotherapy over 6 months (weighted mean difference [WMD] 0.08 [favouring co-cyprindiol], 95% confidence interval [CI] −0.33 to 6.66, p=0.08).

Harborne et al. (2003) (n=52, outcomes available for 34 women) found a statistically significant reduction in Ferriman-Gallwey score with metformin monotherapy compared with co-cyprindiol monotherapy over 12 months (p<0.01) but the absolute reductions were not reported and so could not be incorporated into the meta-analysis with the other 2 RCTs. Harborne et al also found a statistically significant reduction in the women's own assessment of their hirsutism (p=0.01)

Elter et al. (2002) (n=40, outcomes available for all women) found no statistically significant difference in hirsutism with metformin plus co-cyprindiol compared with co-cyprindiol alone over 4 months (p value not stated).

Acne

Harborne et al. (2003) used a patient-self-assessed acne score, which ranged from 0–10. Over 12 months there was no statistically significant difference in acne score between metformin monotherapy and co-cyprindiol (p=0.36).

Menstrual regularity

The Cochrane meta-analysis of two RCTs (Morin-Papunen et al. 2000 and Morin-Papunen et al. 2003) found metformin to be statistically significantly less effective than co-cyprindiol in improving menstrual regularity (Peto odds ratio [OR] 0.08 [favouring co-cyprindiol], 95% CI 0.01 to 0.45, p=0.004).

Other clinical outcomes

Only 1 RCT reported on the development of type 2 diabetes in women with PCOS (Morin-Papunen et al. 2000). Data were available for 18 women over a 6-month period). No difference was seen in the development of type 2 diabetes between the metformin and the co-cyprindiol groups (the Cochrane authors state the Peto OR as 0.17, 95% CI 0.00 to 8.54, p=0.37). None of the RCTs reported the effects of metformin on the risk of cardiovascular events or endometrial cancer events in women with PCOS.

Randomised controlled trials published after the Cochrane review

Cetinkalp et al. (2009)

In this study, women with PCOS (age not stated) were randomised to receive metformin 2000 mg daily or co-cyprindiol. A third group received rosiglitazone; results for this group are not reported here. Data were analysed for women who completed the 4-month study (6 women were lost to follow-up; group allocation was not stated). The allocation method was not discussed and the study appears to have been open label. No power calculation was reported.

Hirsutism (assessed using the Ferriman–Gallwey score) improved to a statistically significant extent in the metformin group (n=47, mean reduction score 2.16 points from 12.71 at baseline, $p<0.05$) and in the co-cyprindiol group (n=33, mean reduction 3.04 points from 15.07 at baseline, $p<0.05$), with no difference in the rate of improvement between groups ($p=0.475$). Acne (measurement scale not reported) improved across all groups from baseline, although this was not found to be statistically significant and there were no statistically significant differences between groups (p values not reported). All women in the trial who had oligomenorrhoea (less than 8 menstrual cycles annually) at baseline reported a statistically significant improvement in menstrual cycle length after 4 months of treatment ($p<0.05$ for each group), although there was no statistically significant difference between groups ($p=0.202$).

Luque-Ramirez et al. (2007)

In this study, 34 women (average age 24±6 years) with PCOS were randomised to receive metformin 850 mg twice daily (n=19) or co-cyprindiol (n=15) for 24 weeks. No women who were taking co-cyprindiol left the study, however 7 women who were taking metformin did and were lost to follow-up (2 because of adverse effects, 2 because of protocol violation and 1 because she became pregnant). Data were analysed on an intention to treat (ITT) basis with last observation carried forward: this was the baseline observation in 5 women taking metformin and none of those taking co-cyprindiol. Analysis was also undertaken on data from the participants who completed the 4 month study. Allocation concealment was unclear and the study was open label. A power calculation was conducted based on an outcome of changes in fasting insulin levels: this suggests that the study was underpowered for that outcome.

Hirsutism (assessed using the Ferriman–Gallwey score) statistically significantly improved in both groups ($p<0.05$, absolute data not reported). The between-group difference was not statistically significant in the analysis restricted to women who completed the 4-month study but was statistically significant in favour of co-cyprindiol ($p<0.05$) in the ITT analysis. Effects on acne were

not assessed. After 24 weeks, menstrual regularity was restored in 50% of women receiving metformin and in all women receiving co-cyprindiol (p value not stated).

Meyer et al. (2007)

In this study, 110 women with PCOS who were also overweight (BMI greater than 27 kg/m^2; mean age 31 years) were randomised to receive metformin 1000 mg twice daily, co-cyprindiol, or combination therapy with an oral contraceptive (ethinylestradiol 20 micrograms with levonorgestrel 100 micrograms) plus spironolactone 50 mg twice daily. Data were analysed for those women who completed the 6-month study (n=100). The allocation method was not discussed and the study was open label. A power calculation was reported that suggests the study was adequately powered for the primary outcome of changes in insulin resistance.

Hirsutism (assessed using the Ferriman–Gallwey score) improved in the metformin group (n=36) from a mean of 8.80 at baseline to a mean of 6.1 at 6 months ($p<0.05$). Improvements in the other groups were also statistically significant but between-group differences were not. Acne was not assessed as an outcome. Menstrual cycle length reduced in the metformin group from a mean of 112 days at baseline to 65 days at 6 months. Improvements in the other groups were also statistically significant but between-group differences were not.

Wu et al. (2008)

In this study, 60 women with PCOS (mean age 25 years, range 19–35 years) were randomised in equal numbers to receive co-cyprindiol only, metformin 500 mg 3 times daily, or a combination of both these treatments. Women were stratified into obese (BMI greater than 25 kg/m^2) or non-obese (BMI less than 25 kg/m^2) groups, and the proportion of obese and non-obese women was similar in all treatment groups. Analyses were based on the women who completed the study (n=53) and by obesity subgroup within each treatment allocation. The allocation method was not discussed. The study was single blind (the clinical outcome assessor was blind to the treatment allocation). No power calculation was reported.

Hirsutism (assessed using the Ferriman–Gallwey score) improved in the co-cyprindiol and co-cyprindiol plus metformin groups to a statistically significant extent (by a mean of 0.9–1.9 points on the Ferriman–Gallwey score from a baseline of 7.8–8.3) but not in the metformin monotherapy group (mean difference 0.2–0.4 points from a baseline of 7.6–8.1), but the between-group statistical significance was not reported. Menstrual regularity was fully restored in all women receiving co-cyprindiol or co-cyprindiol plus metformin, but in only approximately 28% of those receiving metformin (between-group statistical significance not reported).

Evidence: safety

The metformin summary of product characteristics notes that during initiation of treatment with metformin the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These resolve spontaneously in most people.

In the 3 RCTs included in the Cochrane review that compared metformin monotherapy with co-cyprindiol (Morin-Papunen et al. 2000, Harborne et al. 2003 and Morin-Papunen et al. 2003), metformin caused a significantly higher incidence of severe gastrointestinal adverse effects that resulted in medication being stopped (Peto OR 7.75, p=0.02, 95% CI 1.32 to 45.71) and a significantly lower incidence of other severe adverse events that resulted in medication being stopped (weight gain, high blood pressure, depression, chest pain and headache; Peto OR 0.11, p=0.0008, 95% CI 0.03 to 0.39).

The RCT comparing metformin plus Cilest (oral contraceptive containing ethinylestradiol 35 micrograms plus norgestimate 250 micrograms) with Cilest monotherapy (Cibula et al. 2005) found no difference between the treatments in the rate of severe gastrointestinal adverse effects that resulted in medication being stopped (p=0.49). The RCT comparing metformin plus co-cyprindiol with co-cyprindiol (Elter et al. 2002) reported minor adverse effects and no difference was seen between the groups (p=0.11).

Cetinkalp et al. (2009) did not report details of adverse effects. Luque-Ramirez et al. (2007) reported mild to moderate gastrointestinal adverse effects in 2 out of 19 women receiving metformin, who stopped treatment. No adverse effects were reported for women receiving co-cyprindiol. Meyer et al. (2007) reported that 1 woman in the co-cyprindiol group and 1 woman in the ethinylestradiol/levonorgestrel/spironolactone group stopped treatment because of mood swings; adverse effects were not reported in the metformin group. Wu et al. (2008) reported mild to moderate gastrointestinal problems with metformin monotherapy that affected 2 of 20 women (these women did not need to stop treatment); however, moderate gastrointestinal problems in 4 out of 20 women receiving metformin plus co-cyprindiol led them to leave the study.

Evidence: economic issues

Cost effectiveness

No cost-effectiveness studies were identified.

Cost

Metformin is available as standard-release and modified-release tablets. Modified-release tablets are sometimes prescribed in an attempt to reduce the gastrointestinal adverse effects of metformin.

Drug and usual dosage[a]	Annual cost[b]
Metformin 500 mg 3 times a day	£30.03
Metformin 1000 mg twice a day	£40.04
Metformin modified-release 750 mg twice a day	£83.20
Co-cyprindiol 1 daily for 21 days each month	£20.67
[a] The dosages shown are taken from the relevant summary of product characteristics, but do not represent the full range that can be used nor do they imply therapeutic equivalence. [b] Costs taken from Drug Tariff January 2013, based on 13×28-day months per year.	

Current drug usage

It is not possible to determine the indications for which metformin is prescribed, therefore no information on prescribing rates of metformin for PCOS is available.

Evidence strengths and limitations

None of the RCTs considered in this evidence summary compared metformin, alone or in combination, with placebo; most compared it with co-cyprindiol. None of the RCTs was double blind. Three of the RCTs reported significant differences between baseline characteristics of the treatment and control groups despite randomisation and concealment (Cibula et al. 2005, Morin-Papunen et al. 2000 and Morin-Papunen et al. 2003). Allocation was concealed in 4 RCTs but allocation concealment was unclear or not stated in others. The studies showed a significant degree of heterogeneity in terms of treatment duration, assessment methods and inclusion criteria. The trials were predominantly of short duration, with only 1 trial (Harborne et al. 2003) longer than 6 months, and all were small.

Although improvement in hirsutism from baseline was statistically significant in most of the trials, mean absolute reductions in the 36-point Ferriman–Gallwey scores were 2–3 points or less, so these changes may have limited clinical significance for women with PCOS. Effects on acne were

reported in only 2 RCTs (Harborne et al. 2003 and Cetinkalp et al. 2009) and the method of reporting makes drawing conclusions difficult. Only 1 of the RCTs assessed the effect of metformin on development of type 2 diabetes, but this was in only a small number of women over 6 months; none of the RCTs assessed cardiovascular events or endometrial cancer events. Long-term comparison effects on these clinical outcomes as well as hirsutism and acne are lacking.

Summary for patients

A summary written for patients is available on the NICE website.

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Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The interim process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

The sources are:

1. NHS Evidence (including guidelines)
2. NICE
3. Broad internet search: Google, for example, (*metformin or glucophage)* AND *polycystic ovary syndrome* AND (~guideline OR ~algorithm) filetype:pdf

Medline & Embase (via Ovid)

1. (metformin or glucophage or dimethylbiguanidine or dimethylguanylguanidine or metsol).tw.
2. Metformin/
3. 1 or 2
4. Polycystic Ovary Syndrome/
5. (pcos or (polycystic adj ovar*) or (sclerocystic adj ovar*) or (Stein-Leventhal adj syndrome)).tw.

6. 4 or 5
7. 3 and 6
8. exp review/
9. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh.
10. ((hand adj2 search$) or (manual$ adj2 search$)).ti,ab,sh.
11. ((electronic or bibliographic or computeri?ed or online) adj4 database$).ti,ab.
12. (pooling or pooled or mantel haenszel).ti,ab,sh.
13. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh.
14. or/9-13
15. 8 and 14
16. Meta Analysis/
17. (meta-analys$ or meta analys$ or metaanalys$).ti,ab,sh.
18. ((systematic$ or quantitativ$ or methodologic$) adj5 (review$ or overview$ or synthesis$)).ti,ab,sh.
19. (integrative research review$ or research integration).ti,ab,sh.
20. or/16-19
21. 15 or 20
22. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/
23. (random$ or placebo$ or ((singl$ or double$ or triple$ or treble$) and (blind$ or mask$))).ti,ab,sh.
24. 22 or 23
25. (animal$ not human$).sh.
26. 24 not 25

27. (economic? or cost?).tw.
28. 21 or 26
29. 7 and 28
30. 7 and 27
31. 29 or 30
32. limit 31 to english language

CRD HTA, DARE and EED database

1. (metformin or glucophage or dimethylbiguanidine or dimethylguanylguanidine or metsol)
2. MeSH DESCRIPTOR metformin EXPLODE ALL TREES
3. MeSH DESCRIPTOR Polycystic Ovary Syndrome EXPLODE ALL TREES
4. ((polycystic NEXT ovar*) OR (sclerocystic NEXT ovar*) OR (Stein-Leventhal NEXT Syndrome) OR pcos)
5. #1 OR #2
6. #3 OR #4
7. #5 AND #6

Cochrane CENTRAL

1. (metformin or glucophage or dimethylbiguanidine or dimethylguanylguanidine or metsol):ti,ab,kw
2. MeSH descriptor: [Metformin] this term only
3. #1 or #2
4. (pcos or (polycystic next ovar*) or (sclerocystic next ovar*) or (Stein-Leventhal next syndrome)):ti,ab,kw
5. MeSH descriptor: [Polycystic Ovary Syndrome] this term only
6. #4 or #5

7. #3 and #6 in Cochrane Reviews (Reviews only) and Trials

Euroscan

metformin or glucophage

Grey literature and ongoing trials search

1. FDA
2. EMA
3. MHRA
4. Scottish Medicines Consortium
5. All Wales Medicine Strategy Group
6. Manufacturers' websites as applicable
7. metaRegister of Controlled Trials (mRCT)
8. ClinicalTrials.gov

Manufacturers' websites

Bristol-Myers Squibb

Merck Serono

Evidence selection

Studies were included based on predetermined criteria for relevance to the question set at scoping. Individual studies were scored for validity using the methods and checklists described in the appendices of the NICE guidelines method manual. The highest quality research was selected as the basis for answering the questions set on efficacy, safety and cost.

Changes since publication

March 2013: footnote b in the table in the Evidence: economic issues section has had the date corrected from January 2012 to January 2013.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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