

AHRQ Systematic Review Surveillance Program

CER #41: Noncyclic Chronic Pelvic Pain Therapies for Women: Comparative Effectiveness

Original Release Date: January, 2012

Surveillance Report: October, 2012

Surveillance Report: October, 2015

Summary of Key Findings from Surveillance Report:

- Key Question 1: Original systematic review conclusions are valid.
- Key Question 2: New studies were identified evaluating the long-term effectiveness of surgical interventions; however, the new evidence does not change the conclusions of the original systematic review.
- Key Question 3: Original systematic review conclusions are valid.
- Key Question 4: Conclusions related to non-hormonal, non-pharmaceutical interventions may not be current. A new systematic review was identified which found that transvenous occlusion is effective in reducing pelvic pain. No evidence related to transvenous occlusion was included in the original systematic review. All other conclusions are valid.
- Key Question 5. Original systematic review conclusions are valid.

Signal Assessment: The signals examined in this surveillance assessment suggest that the some conclusions of the original report may not be current.

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Conflict of Interest:

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Introduction

The purpose of the surveillance process for the EPC Program is to decide if the findings of a systematic review are current. Approximately 25 systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #41 titled “Noncyclic Chronic Pelvic Pain Therapies for Women: Comparative Effectiveness” was originally released in January, 2012.¹

The key questions for the original systematic review are as follows:

Key Question 1. Among women who have been diagnosed with noncyclic/mixed cyclic and noncyclic CPP, what is the prevalence of the following comorbidities: dysmenorrhea, major depressive disorder, anxiety disorder, temporomandibular joint pain disorder, fibromyalgia, IBS, interstitial cystitis (IC)/painful bladder syndrome (PBS), complex regional pain syndrome, vulvodynia, functional abdominal pain syndrome, low back pain, headache, and sexual dysfunction?

Key Question 2. Among women with noncyclic/mixed cyclic and noncyclic CPP, what is the effect of surgical interventions on pain status, functional status, satisfaction with care, and quality of life?

Key Question 3. What is the evidence that surgical outcomes differ if the etiology of noncyclic/mixed cyclic and noncyclic CPP is identified after surgery?

Key Question 4. Among women with noncyclic/mixed cyclic and noncyclic CPP, what is the effect of nonsurgical interventions on pain status, functional status, satisfaction with care, quality of life, and harms?

Key Question 5. What is the evidence for choosing one intervention over another to treat persistent or recurrent noncyclic/mixed cyclic and noncyclic CPP after an initial intervention fails to achieve target outcome(s)?

Our surveillance assessment began in July 2015. We conducted an electronic search for literature published since the end date of the most recent surveillance report search date. After completing a scan of this literature to identify evidence potentially related to the key questions in this systematic review, we contacted experts involved in the original systematic review to request their opinions as to whether the conclusions had changed.

Methods

Prior Surveillance

A surveillance report for the original systematic review was released in October 2012, and included a search for relevant literature published between May 2011 and July 2012, expert opinion, and a search of U.S. Food and Drug Administration (FDA) reports.² The findings from this report are included in our assessment.

Literature Searches

We conducted a literature search of PubMed covering July 2012 to July 2015, using the identical search strategy used for the original systematic review¹ and searching for studies published since the end date of the most recent surveillance search.

The search was conducted to assess the currency of conclusions using journals from among the top 10 journals from relevant specialty subject areas and among those most highly represented among the references for the original report. We included the journals searched in the previous surveillance assessment. The included journals were six high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Cochrane Database of Systematic Reviews, Journal of the American Medical Association, Lancet, and New England Journal of Medicine), and five specialty journals (American Journal of Obstetrics and Gynecology, European Journal of Obstetrics and Gynecology and Reproductive Biology, Fertility and Sterility, Journal of Obstetrics and Gynecology, and Obstetrics and Gynecology). The search strategy is reported in Appendix A.

Study Selection

Using the same inclusion and exclusion criteria as the original systematic review (see Appendix B), one investigator reviewed the titles and abstracts of the 11 high-impact journal search results (Appendix C).

Expert Opinion

We shared the conclusions of the original report and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with ten experts in the field (original peer reviewers, technical expert panel members [TEP], and a local expert) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Four subject matter experts responded to our request. Appendix D shows the form experts were asked to complete.

Horizon Scanning

The AHRQ Healthcare Horizon Scanning System identifies emerging health care technologies and innovations with the potential to impact health care for AHRQ's 14 priority conditions.³ We reviewed the Pregnancy, including Preterm Birth section to identify new potentially high-impact interventions related to the key questions in this systematic review. Potentially high impact interventions were considered in the final assessment of the need to update.

FDA Black Box Warnings

We searched the FDA MedWatch online database website for black box warnings relevant to the key questions in this systematic review.

Check for Qualitative Signals

The authors of the original systematic review conducted qualitative synthesis of data on the prevalence of comorbid conditions in women with noncyclic/mixed cyclic and non cyclic chronic pelvic pain, the effect of surgical and nonsurgical interventions on pain and functional status, satisfaction with care, and quality

of life – and whether outcomes differ if the etiology of noncyclic/mixed cyclic and non cyclic chronic pelvic pain is identified after surgery, as well as the evidence related to choosing an intervention after an initial intervention has failed. We compared the conclusions of the included abstracts to the conclusions of the original systematic review and previous surveillance report, and assessed expert opinions to identify qualitative signals about the currency of conclusions.

Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix E) that includes the key questions, the conclusions from the original systematic review and most recent surveillance assessment, findings of the new literature search, and the expert assessments that pertained to each key question. Because we did not find any FDA black box warnings relevant to the key questions in this systematic review, we did not include a column for this in the summary table. We categorized the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the systematic review is likely current
- Original conclusion is possibly out of date and this portion of the systematic review may not be current
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the systematic review conclusion as still valid, we classified the systematic review conclusion as likely current.
- If we found some new evidence that might change the systematic review conclusion, and /or a minority of responding experts assessed the systematic review conclusion as having new evidence that might change the conclusion, then we classified the systematic review conclusion as may not be current.
- If we found new evidence that rendered the systematic review conclusion out of date or no longer applicable, we classified the systematic review conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

Signal Assessment for Currency of the Systematic Review

We used the following considerations in our assessment of currency of the systematic review:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original report out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal when new evidence is identified which may change the conclusions from the original report. This may occur when abstract review and expert assessment indicates that some conclusions from the original report may be out of date, or when it is unclear from abstract review how new evidence may impact the findings from the original systematic review.
- **Weak signal:** A report is considered to have a weak signal if little or no new evidence is identified that would change the conclusions from the original systematic review. This may occur

when little to no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original systematic review.

Results

Prior Surveillance

Prior surveillance of the topic included two studies and consultation with two subject matter experts, and concluded that all original systematic review conclusions were determined to be current.²

Literature Search

The literature search identified 36 unique titles from the 11 selected high profile general medical and specialty journals (Appendix C). Upon abstract review, 31 studies were rejected because they did not meet the original CER inclusion criteria (see Appendix B). The remaining 5 studies⁴⁻⁸ were examined for potential to change the results of the original review.

Horizon Scanning

None of the interventions in the horizon scanning report for Priority Area 12: Pregnancy and Preterm Birth overlapped with the key questions in the original systematic review. Thus, we did not identify new interventions with high-impact potential for this topic.

FDA Black Box Warnings

We did not find any FDA black box warnings relevant to the key questions in this systematic review.

Expert Opinion

We shared the conclusions of the original systematic review with ten experts in the field (original peer reviewers, TEP members and a local expert) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Four subject matter experts responded.

One expert believed all systematic review conclusions to be current. Three experts identified at least one conclusion they felt was out of date, or did not know. Two reviewers felt that there were likely studies related to the key questions, but did not suggest specific studies. One reviewer recommended 22 studies^{6,9-29}, of which 12⁹⁻²⁰ were excluded due to population or outcome criteria, and one⁶ was already identified in our literature search. Three studies^{25-26, 28} were included (see Appendix E).

Identifying Qualitative Signals

Appendix E shows the original key questions, the conclusions of the original systematic review and the most recent surveillance report, the results of the literature search, the experts' opinion, and the assessment of the currency of the systematic review.

For Key Question 1, regarding the prevalence of comorbidities, all original systematic review conclusions are likely current. For Key Question 2, while the conclusions regarding the similarity in the effectiveness of surgical interventions are likely current, no studies included in the original systematic review included a follow up longer than 12 months. Two studies identified by one of our expert reviewers examined long-term outcomes. In one cohort follow up study, patients reported significant improvement in pelvic pain for a mean duration of 54 months after laparoscopic bowel resections for deep infiltrating endometriosis. In addition, a prospective cohort study²⁸ found significant improvement in quality of life and the visual analogue scale associated with CO2 laser ablative surgery with and without bowel resection. All conclusions related to Key Question 3 are likely current.

For Key Question 4, conclusions regarding non-hormonal, non-pharmaceutical interventions may not be current. The original systematic review did not include evidence regarding the effectiveness of transvenous occlusion. We identified one systematic review⁵ of 13 studies of poor methodological quality in which statistically significant improvements in pelvic pain were reported in 9 of the 13 studies, with subjective improvements in pain reported in all 13 studies. All other Key Question 4 conclusions are likely up to date. We identified no studies with the potential to change the conclusions for Key Question 5. There were no new high-impact potential interventions for this report based on horizon scanning data, and no FDA boxed warnings were identified since the original report was published.

Signal Assessment

The SRC conclusions based on the results of the prior surveillance assessment, literature published since the original report, FDA boxed warnings, horizon scanning, and expert assessment is that:

- Key Question 1: Original systematic review conclusions are valid
- Key Question 2: Original systematic review conclusions are valid. However there is new evidence regarding the long-term effectiveness of surgical interventions.
- Key Question 3: Original systematic review conclusions are valid.
- Key Question 4: Conclusions about non-hormonal, non-pharmaceutical interventions may not be current due to findings that transvenous occlusion is effective in reducing pelvic pain. All other conclusions are valid.
- Key Question 5: Original systematic review conclusions are valid.

The signal for this report is medium, suggesting that some conclusions in the original systematic review may not be current.

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Appendices

Appendix A: Original Search Strategy

Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review

Appendix C: Literature Search Results

Appendix D: Questionnaire Sent to Expert Reviewers

Appendix E: Summary Table

Appendix A. Search Strategy

PubMed was searched on July 10, 2015

| | |
|---|------------------------------------|
| PubMed was searched on July 10, 2015 | |
| Search (((((((("chronic pelvic pain") OR (((((((("pelvic pain" OR pelvic pain[mh]))) OR (((musculoskeletal diseases[mh] OR myofascial[tiab]) AND (pelvic[tiab] OR pelvis[tiab] OR pelvis[mh] OR pelvic pain[tiab])))) AND (((chronic OR recurrent OR recurring OR chronic disease[mh] OR noncyclic OR non-cyclic OR mixed)))))) NOT (((("Case Reports"[Publication Type]) OR "Letter"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type]) OR "Practice Guideline"[Publication Type]))) | Original Search |
| AND ("2012/07/12"[Date - Entrez] : "3000"[Date - Entrez])) | Date Limit |
| AND (((((((("Annals of internal medicine"[Journal]) OR "BMJ (Clinical research ed.)"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "JAMA"[Journal]) OR "Lancet (London, England)"[Journal]) OR "The New England journal of medicine"[Journal])) | Journal Limit : General Medicine |
| OR (((((((("American journal of obstetrics and gynecology"[Journal])) OR ("European journal of obstetrics, gynecology, and reproductive biology"[Journal])) OR ("Fertility and sterility"[Journal])) OR ("American journal of obstetrics and gynecology"[Journal])) OR ("Obstetrics and gynecology"[Journal])) | Journal Limit : Specialty Journals |

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Appendix B. Inclusion and Exclusion Criteria from Original Systematic Review

| Category | Criteria |
|---|--|
| Study population | Adult women (≥ 18 years of age) with noncyclic or mixed cyclic/noncyclic chronic pelvic pain undergoing surgical or nonsurgical treatment |
| Time period | 1990-May 3, 2011 |
| Publication languages | English only |
| Admissible evidence (study design and other criteria) | <p><u>Admissible designs</u></p> <ul style="list-style-type: none"> Controlled trials, prospective cohort studies with $N \geq 50$, cross-sectional studies Case series with $N \geq 100$ and harms or prevalence data relevant to the KQs <p><u>Other criteria</u></p> <ul style="list-style-type: none"> Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results Patient populations must include adult women (≥ 18 years of age) being treated for CPP; studies with a primary focus on coexisting conditions (vulvodynia, irritable bowel syndrome, etc.) or on cancer pain or pregnancy-related pain be excluded Studies must include at least one outcome measure of an outcome listed in the PICOTS Studies must address one or more of the following CPP: <ul style="list-style-type: none"> Treatment modality aimed at modifying CPP symptoms Short- and long-term outcomes (including non-surgical harms) related to treatment for symptoms of CPP Studies must include extractable data on relevant outcomes Sample sizes must be appropriate for the study question addressed in the paper |

Abbreviations: CPP = noncyclic chronic pelvic pain; KQ = Key Question; N = number; PICOTS = population, intervention, comparison, outcomes, timing, setting.

Appendix C. Literature Search Results

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Appendix D. Questionnaire Sent to Expert Reviewers

AHRQ Comparative Effectiveness Review Surveillance Program

Reviewer Form

Title of Original Review: Noncyclic Chronic Pelvic Pain Therapies for Women: Comparative Effectiveness

[Link to Report](#)

[Link to Surveillance](#)

Name of Reviewer: _____

Instructions:

The AHRQ Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ reviews to assist with prioritization of reports for updating. One part of this process includes soliciting expert review of our synthesis of recently published literature and any identified FDA black box warnings.

The attached document includes a table highlighting the conclusions from the original report, conclusions from a surveillance review conducted in 2012, and our synthesis of the recently published literature. Abstracts from relevant literature are included at the end of the attached document. If you would like a list of our full search results, please let us know.

Please review the table in the attached document and provide responses to the questions for each key question below. The primary goal of this review is to identify any missing studies, drugs, interventions, or devices; and ensure the accuracy of our synthesis of the recently published literature.

Key Question 1:

Among women who have been diagnosed with noncyclic/mixed cyclic and noncyclic CPP, what is the prevalence of the following comorbidities:

- Dysmenorrhea
- Major depressive disorder
- Anxiety disorder
- Temporomandibular joint pain disorder
- Fibromyalgia
- Irritable Bowel Syndrome
- Interstitial cystitis (IC)/painful bladder syndrome (PBS)
- Complex regional pain syndrome
- Vulvodynia
- Functional abdominal pain syndrome
- Low back pain
- Headache
- Sexual dysfunction

Prior Surveillance Assessment (October 2012):

- All conclusions were up-to-date

SRC Literature Analysis:

- One cross sectional study found that among women who menstruate regularly, those with dysmenorrhea had disproportionately more severe noncyclic pelvic pain than women without dysmenorrhea.
- One prospective cohort study found that women with deep endometriosis related pain (dysmenorrhea, pelvic pain, dyspareunia) showed the highest level of perceived stress.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 2:

Among women with noncyclic/mixed cyclic and noncyclic CPP, what is the effect of surgical interventions on pain status, functional status, satisfaction with care, and quality of life?

Prior Surveillance Assessment (October 2012):

- All conclusions were up to date

SRC Literature Analysis:

- One prospective cohort study found that after surgery for endometriosis, perceived stress significantly decreased.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 3:

What is the evidence that surgical outcomes differ if the etiology of noncyclic/mixed cyclic and noncyclic CPP is identified after surgery?

Prior Surveillance Assessment (October 2012):

- All conclusions were up to date

SRC Literature Analysis:

- No new literature was found.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 4:

Among women with noncyclic/mixed cyclic and noncyclic CPP, what is the effect of nonsurgical interventions on pain status, functional status, satisfaction with care, quality of life, and harms?

Prior Surveillance Assessment (October 2012):

- All conclusions were up to date

SRC Literature Analysis:

- One systematic review of thirteen studies including 866 women undergoing trans-venous occlusion of pelvic veins for CPP found statistically significant improvements in pelvic pain were reported in nine of the 13 studies. Technical success was reported in 865 of 866 (99.8%) with low complication rates: coil migration in 14 women (1.6%), abdominal pain in ten women (1.2%) and vein perforation in five (0.6%). In a study on varicose veins of the legs, recurrence was seen in 13% of 179 women 5-years following coil embolization. Subjective improvements in pain were seen in all 13 studies after treatment by trans-venous occlusion.
- A systematic review (Cheong et al., 2015) found that the estimated effect of lofexidine on pain outcomes when compared with placebo was compatible with benefit and harm. Women in the lofexidine group reported more adverse effects than women given placebo.
- A systematic review (Cheong et al., 2015) found head-to-head comparisons showed that women taking goserelin had greater improvement in pelvic pain score at one year than those taking progestogen. Women taking gabapentin had a lower VAS pain score than those taking amitriptyline. Study authors reported that no statistically significant difference was observed in the rate of adverse effects among women taking gabapentin compared with women given amitriptyline.
- A systematic review (Cheong et al., 2015) found that women who underwent reassurance ultrasound scans and received counseling were more likely to report improved pain than those treated with a standard 'wait and see' policy. Significantly more women who had writing therapy as a disclosure reported improvement in pain than those in the non-disclosure group. No difference between groups in pain outcomes was noted when other psychological therapies were compared with standard care or placebo.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 5:

What is the evidence for choosing one intervention over another to treat persistent or recurrent noncyclic/mixed cyclic and noncyclic CPP after an initial intervention fails to achieve target outcome(s)?

Prior Surveillance Assessment (October 2012):

- All conclusions were up to date

SRC Literature Analysis:

- No new literature was found.

Reviewer Questions:

3. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

4. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Original Review Conclusions and Literature Analysis

Title of Original Review: Noncyclic Chronic Pelvic Pain Therapies for Women: Comparative Effectiveness

[Link to Report](#)

[Link to Surveillance](#)

The conclusions from the original report, conclusions from a prior surveillance assessment and an analysis of recent literature identified by the Scientific Resource Center (SRC) are summarized below. Abstracts are provided for included literature at the end of the document.

| Conclusions From Original CER | Conclusions from Prior Surveillance Assessment (Oct 2012) | Current Literature Analysis (July 2015) |
|--|---|---|
| Key Question 1: Prevalence and Comorbidities | | |
| Noncyclic CPP was variably defined, and diagnostic approaches were rarely reported. [Key finding] | The conclusions are still valid. | No new literature was identified |
| Disproportionately few studies addressed noncyclic CPP, given the prevalence of the condition. [Key finding] | The conclusions are still valid. | No new literature was identified |
| Comorbidities were similarly variably defined and frequently not diagnosed using standardized criteria. [Key finding] | The conclusions are still valid. | No new literature was identified |
| Dysmenorrhea, dyspareunia, and IBS were the most frequently reported comorbidities in the literature meeting our criteria. [Key finding] | The conclusions are still valid. | <p>A cross sectional study found that among women who menstruate regularly, those with dysmenorrhea had disproportionately more severe noncyclic pelvic pain (54/402, 13%) than women without dysmenorrhea (5/432, 1%; odds ratio, 13; 95% confidence interval, 5-33). In a multivariate-adjusted model, dysmenorrhea (beta = .17), activity capability (beta = .17), somatic complaint (beta = .17), and bodily pain (beta = .12) were the primary predictors of noncyclic pelvic pain. Depression (beta = .03) and anxiety (beta = .01) were not significantly predictive. The presence of dysmenorrhea, somatic complaint, and low activity capability predicted 90% of the cases of women with noncyclic pelvic pain.</p> <p>One prospective cohort study found that women with</p> |

| Conclusions From Original CER | Conclusions from Prior Surveillance Assessment (Oct 2012) | Current Literature Analysis (July 2015) |
|--|---|--|
| | | deep endometriosis related pain (dysmenorrhea, pelvic pain, dyspareunia) showed the highest level of perceived stress. |
| Key Question 2. Outcomes of Surgical Interventions for CPP | | |
| Intervention studies overall included a limited number of participants and typically included only short-term follow-up. [Key finding] | The conclusions are still valid. | No new literature was identified |
| Few studies of surgical approaches examined the same approach; none used a placebo control. [Key finding] | The conclusions are still valid. | No new literature was identified |
| No surgical approach was superior to a nonsurgical approach or comparative surgical approach. [Key finding] | The conclusions are still valid. | No new literature was identified |
| The strength of the evidence for surgical approaches overall was insufficient to low. [Key finding] | The conclusions are still valid. | No new literature was identified |
| Among studies addressing treatment effects, little evidence demonstrates the effectiveness of surgical approaches. Despite numerous surgical techniques used extensively in treating CPP, few studies included more than 50 participants, and few were considered high quality. All of the studies with comparison data failed to demonstrate that surgery in general or any specific surgical technique was more efficacious than either nonsurgical intervention or the comparator technique in improving pain status in patients. No surgical technique was superior, and the evidence to conclude that surgical intervention is either effective or ineffective for the treatment of CPP is insufficient. [Conclusion] | The conclusions are still valid. | One prospective cohort study found that after surgery for endometriosis, perceived stress significantly decreased. |
| Intervention studies overall included a limited number of participants and typically included only short-term followup. [Key finding] | The conclusions are still valid. | No new literature was identified |
| Key Question 3: Evidence for Differences in Surgical Outcomes by Etiology | | |

| Conclusions From Original CER | Conclusions from Prior Surveillance Assessment (Oct 2012) | Current Literature Analysis (July 2015) |
|---|---|--|
| No studies addressed evidence for differences in outcomes by etiology. [Key finding] | The conclusions are still valid. | No new literature was identified |
| Key Question 4: Outcomes of Nonsurgical Interventions for CPP | | |
| Most studies of nonsurgical approaches meeting our criteria addressed hormonal approaches and included women with endometriosis-associated CPP. [Key finding] | The conclusions are still valid. | No new literature was identified |
| Few studies of nonsurgical interventions were placebo controlled, and few addressed nonpharmacologic approaches; strength of evidence was insufficient to low. [Key finding] | The conclusions are still valid. | A systematic review (Cheong et al., 2015) found that the estimated effect of lofexidine on pain outcomes when compared with placebo was compatible with benefit and harm (Peto OR 0.42, 95% CI 0.11 to 1.61, one study, 39 women, low-quality evidence). Women in the lofexidine group reported more adverse effects (including drowsiness and dry mouth) than women given placebo (moderate-quality evidence). Head-to-head comparisons showed that women taking goserelin had greater improvement in pelvic pain score (MD 3, 95% CI 2.08 to 3.92, one study, n = 47, moderate-quality evidence) at one year than those taking progestogen. Women taking gabapentin had a lower VAS pain score than those taking amitriptyline (MD -1.50, 95% CI -2.06 to -0.94, n = 40, low-quality evidence). Study authors reported that no statistically significant difference was observed in the rate of adverse effects among women taking gabapentin compared with women given amitriptyline. |
| Hormonal studies reported equal effectiveness among the active agents investigated, with the exception of a placebo-controlled trial of raloxifene reporting more rapid return of pain in the raloxifene group. [Key finding] | The conclusions are still valid. | A systematic review (Cheong et al., 2015) found two studies reporting that progestogen was more effective than placebo in women achieving > 50% reduction in visual analogue scale pain score immediately after treatment (Peto OR 3.00, 95% CI 1.70 to 5.31, two studies, n = 204, I(2) = 22%, moderate-quality evidence). Evidence of benefit was maintained up to nine months after treatment (Peto OR 2.09, 95% CI 1.18 to 3.71, two studies, n = 204, I(2) = 0%, moderate-quality evidence). Women treated with progestogen reported more adverse effects (e.g. weight gain, bloating) than those given |

| Conclusions From Original CER | Conclusions from Prior Surveillance Assessment (Oct 2012) | Current Literature Analysis (July 2015) |
|--|---|---|
| | | <p>placebo (high-quality evidence).</p> <p>A patient preference trial (Morotti et al., 2014) comparing a progestogen only contraceptive pill to a combined contraceptive in women with pain related to endometriosis and migraines found similar reductions in chronic pelvic pain and dyspareunia over 6-months in both groups, with a larger percentage of patient reporting satisfaction in the progestogen only group (61.2% vs. 37.8%), as well as a significant reduction in the number of migraines ($p=.002$). No reduction of migraines were found in the combined group.</p> |
| <p>Studies of nonhormonal and nonpharmacologic agents reported some positive effects on pain status. [Key finding]</p> | <p>The conclusions are still valid, but more studies are available.</p> | <p>One systematic review of thirteen studies including 866 women undergoing trans-venous occlusion of pelvic veins for CPP found statistically significant improvements in pelvic pain were reported in nine of the 13 studies. Technical success was reported in 865 of 866 (99.8%) with low complication rates: coil migration in 14 women (1.6%), abdominal pain in ten women (1.2%) and vein perforation in five (0.6%). In a study on varicose veins of the legs, recurrence was seen in 13% of 179 women 5-years following coil embolization. Subjective improvements in pain were seen in all 13 studies after treatment by trans-venous occlusion. All 13 studies were of poor methodological quality. Complication rates were low and no fatalities occurred.</p> <p>A systematic review (Cheong et al., 2015) found that women who underwent reassurance ultrasound scans and received counselling were more likely to report improved pain than those treated with a standard 'wait and see' policy (Peto OR 6.77, 95% CI 2.83 to 16.19, $n = 90$, low-quality evidence). Significantly more women who had writing therapy as a disclosure reported improvement in pain than those in the non-disclosure group (Peto OR 4.47, 95% CI 1.41 to 14.13, $n = 48$, very low-quality evidence). No difference between groups in pain outcomes was noted when other psychological therapies were compared with standard care or placebo</p> |

| Conclusions From Original CER | Conclusions from Prior Surveillance Assessment (Oct 2012) | Current Literature Analysis (July 2015) |
|---|---|---|
| | | (quality of evidence ranged from very low to low). |
| Few nonsurgical studies reported harms. [Key finding] | The conclusions are still valid. | A systematic review (Cheong et al., 2015) identified no studies of psychological treatments that reported adverse events. |
| Studies of nonsurgical approaches typically addressed hormonal management of endometriosis-related CPP and were not placebo controlled, thus limiting our ability to understand whether hormonal therapies would be beneficial for women with CPP without endometriosis and whether pain relief reported is due simply to the placebo effect. Some studies reported benefits of other nonsurgical approaches, but nonhormonal and nonpharmacologic management remains understudied. [Conclusions] | Overall, the conclusions are still valid but there are now two additional, small placebo-controlled RCTs available in the literature. | No new literature was identified |
| Key Question 5: Evidence for Selecting One Intervention Over Another | | |
| No studies addressed [...] evidence for selecting one intervention over another if an intervention failed. [Key finding] | The conclusions are still valid. | No new literature was identified |

Legend: CPP: chronic pelvic pain; RCT: randomized controlled trial; SCEPC: Southern California Evidence-based Practice Center

Abstracts from Relevant Literature

Cheong, Y. C., Smotra, G. and Williams, A. C. 2014.

Non-surgical interventions for the management of chronic pelvic pain. Cochrane Database Systematic Reviews.

BACKGROUND: Chronic pelvic pain is a common and debilitating condition; its aetiology is multifactorial, involving social, psychological and biological factors. The management of chronic pelvic pain is challenging, as despite interventions involving surgery, many women remain in pain without a firm gynaecological diagnosis. **OBJECTIVES:** To assess the effectiveness and safety of non-surgical interventions for women with chronic pelvic pain. **SEARCH METHODS:** We searched the Menstrual Disorders and Subfertility Group Specialised Register. We also searched (from inception to 5 February 2014) AMED, CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS. We handsearched sources such as citation lists, trial registers and conference proceedings. **SELECTION CRITERIA:** Randomised controlled trials (RCTs) on non-surgical management of chronic pelvic pain were eligible for inclusion. We included studies of women with a diagnosis of pelvic congestion syndrome or adhesions but excluded those with pain known to be caused by endometriosis, primary dysmenorrhoea (period pain), active chronic pelvic inflammatory disease or irritable bowel syndrome. We considered studies of any non-surgical intervention, including lifestyle, physical, medical and psychological treatments. **DATA COLLECTION AND ANALYSIS:** Study selection, quality assessment and data extraction were performed independently by two review authors. Meta-analysis was performed using the Peto odds ratio (Peto OR) for dichotomous outcomes and the mean difference (MD) for continuous outcomes, with 95% confidence intervals (CIs). The primary outcome measure was pain relief, and secondary outcome measures were psychological outcomes, quality of life, requirement for analgesia and adverse effects. The quality of the evidence was assessed by using GRADE methods. **MAIN RESULTS:** Twenty-one RCTs were identified that involved non-surgical management of chronic pelvic pain: 13 trials were included in the review, and eight were excluded. The studies included a total of 750 women-406 women in the intervention groups and 344 in the control groups. Included studies had high attrition rates, and investigators often did not blind adequately or did not clearly describe randomisation procedures. Medical treatment versus placebo Progestogen (medroxyprogesterone acetate (MPA)) was more effective than placebo at the end of treatment in terms of the number of women achieving a greater than 50% reduction in visual analogue scale (VAS) pain score immediately after treatment (Peto OR 3.00, 95% CI 1.70 to 5.31, two studies, n = 204, I(2) = 22%, moderate-quality evidence). Evidence of benefit was maintained up to nine months after treatment (Peto OR 2.09, 95% CI 1.18 to 3.71, two studies, n = 204, I(2) = 0%, moderate-quality evidence). Women treated with progestogen reported more adverse effects (e.g. weight gain, bloatedness) than those given placebo (high-quality evidence). The estimated effect of lofexidine on pain outcomes when compared with placebo was compatible with benefit and harm (Peto OR 0.42, 95% CI 0.11 to 1.61, one study, 39 women, low-quality evidence). Women in the lofexidine group reported more adverse effects (including drowsiness and dry mouth) than women given placebo (moderate-quality evidence). Head-to-head comparisons of medical treatments Head-to-head comparisons showed that women taking goserelin had greater improvement in pelvic pain score (MD 3, 95% CI 2.08 to 3.92, one study, n = 47, moderate-quality evidence) at one year than those taking progestogen. Women taking gabapentin had a lower VAS pain score than those taking amitriptyline (MD -1.50, 95% CI -2.06 to -0.94, n = 40, low-quality evidence). Study authors reported that no statistically significant difference was observed in the rate of adverse effects among women taking gabapentin compared with women given amitriptyline. The study comparing goserelin versus progestogen did not report on adverse effects. Psychological treatment Women who underwent reassurance ultrasound scans and received counselling were more likely to report improved pain than those treated with a standard 'wait and see' policy (Peto OR 6.77, 95% CI 2.83 to 16.19, n = 90, low-quality evidence). Significantly more women who had writing therapy as a disclosure reported

improvement in pain than those in the non-disclosure group (Peto OR 4.47, 95% CI 1.41 to 14.13, n = 48, very low-quality evidence). No difference between groups in pain outcomes was noted when other psychological therapies were compared with standard care or placebo (quality of evidence ranged from very low to low). Studies did not report on adverse effects. Complementary therapy Distension of painful pelvic structures was more effective for pain when compared with counselling (MD 35.8, 95% CI 23.08 to 48.52 on a zero to 100 scale, one study, n = 48, moderate-quality evidence). No difference in pain levels was observed when magnetic therapy was compared with use of a control magnet (very low-quality evidence). Studies did not report on adverse effects. The results of studies examining psychological and complementary therapies could not be combined to yield meaningful results. AUTHORS' CONCLUSIONS: Evidence of moderate quality supports progestogen as an option for chronic pelvic pain, with efficacy reported during treatment. In practice, this option may be most acceptable among women unconcerned about progestogenic adverse effects (e.g. weight gain, bloatedness-the most common adverse effects). Although some evidence suggests possible benefit of goserelin when compared with progestogen, gabapentin as compared with amitriptyline, ultrasound versus 'wait and see' and writing therapy versus non-disclosure, the quality of evidence is generally low, and evidence is drawn from single studies. Given the prevalence and healthcare costs associated with chronic pelvic pain in women, RCTs of other medical, lifestyle and psychological interventions are urgently required.

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Hansrani, V., Abbas, A., Bhandari, S., Caress, A. L., Seif, M. and Mccollum, C. N. 2015.

Trans-venous occlusion of incompetent pelvic veins for chronic pelvic pain in women: a systematic review. Eur J Obstet Gynecol Reprod Biol.

Chronic pelvic pain (CPP) affects 24% of women worldwide; the cause cannot be identified in 40% despite invasive investigations. Dilated, refluxing pelvic veins may be a cause of CPP and treatment by trans-venous occlusion is increasingly performed when gynecological causes are excluded, but is it effective? A systematic review of the literature published between 1966 and July 2014 was conducted. Two authors independently reviewed potential studies according to a set of eligibility criteria, with a third assessor available as an arbiter. Thirteen studies including 866 women undergoing trans-venous occlusion of pelvic veins for CPP were identified (Level of evidence: one study grade 2b, 12 studies grade four). Statistical significant improvements in pelvic pain were reported in nine of the 13 studies. Technical success was reported in 865 of 866 (99.8%) with low complication rates: coil migration in 14 women (1.6%), abdominal pain in ten women (1.2%) and vein perforation in five (0.6%). In a study on varicose veins of the legs, recurrence was seen in 13% of 179 women 5-years following coil embolization. Subjective improvements in pain were seen in all 13 studies after treatment by trans-venous occlusion. All 13 studies were of poor methodological quality. Complication rates were low and no fatalities occurred. Well-designed studies are essential to determine whether pelvic vein incompetence (PVI) is associated with CPP, and to explore whether trans-venous occlusion of PVI improves quality of life for these women.

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Lazzeri, L., Vannuccini, S., Orlandini, C., Luisi, S., Zupi, E., Nappi, R. E. and Petraglia, F. 2015.

Surgical treatment affects perceived stress differently in women with endometriosis: correlation with severity of pain. Fertility and Sterility.

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OBJECTIVE: To investigate the amount of perceived stress in a group of women with different forms of endometriosis-related pain before and after surgical treatment. DESIGN: Prospective clinical trial. SETTING: University hospital. PATIENT(S): A group of women (n = 98) referred to our center for chronic pain and suspected of having endometriosis. INTERVENTION(S): All women suspected of having endometriosis with ultrasonography underwent to a clinical evaluation including assessment of perception of stress. Endometriosis was confirmed histologically by laparoscopy. Painful symptoms and perception of stress were recorded 1 month after surgery. MAIN OUTCOME MEASURE(S): Perceived stress scale (PSS) and visual analog scale for painful symptoms before and 1 month after surgery for endometriosis. RESULT(S): The PSS score before surgery was perceived as "very high" in patients with deep endometriosis (n = 20) or deep endometriosis associated with endometrioma (n = 21); "high" or "medium" PSS was perceived in patients with endometrioma (n = 34) or endometrioma associated with peritoneal endometriosis (n = 23). After the surgical treatment a significant decrease of the "very high" PSS score was shown, as well as when the entire group of patients was considered. When evaluated before and after surgery, according to the severity of pain (dysmenorrhea, dyspareunia, and pelvic pain), a direct correlation was found with the level of PSS. CONCLUSION(S): Patients with deep endometriosis-related pain (dysmenorrhea, pelvic pain, dyspareunia) showed the highest level of perceived stress, which significantly decreased after surgical treatment.

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Morotti, M., Remorgida, V., Venturini, P. L. and Ferrero, S. 2014

Progestogen-only contraceptive pill compared with combined oral contraceptive in the treatment of pain symptoms caused by endometriosis in patients with migraine without aura. European Journal of Obstetrics & Gynecology and Reproductive Biology

OBJECTIVE: Evaluate patient satisfaction at 6-month treatment in women with symptomatic rectovaginal endometriosis and migraine without aura with (progestogen-only contraceptive pill, POP versus sequential combined oral contraceptives, COC) STUDY DESIGN: A patient preference trial including 144 women (82 in the group COC and 62 in the group POP). Main outcome measure was the degree of patient satisfaction by using a Likert scale. Secondary objectives were to evaluate differences in endometriosis-related pain and changes in migraine features during the treatment. RESULTS: In group POP, 38/62 women (61.2%) were satisfied or very satisfied after treatment, compared to 31/82 women (37.8%) in group COC (p=0.005). The intensity of chronic pelvic pain and dyspareunia significantly decreased at 6-month treatment in both the groups. At 6-month treatment, the number of migraine attacks was lower than at baseline in group POP (p=0.002), while it was not reduced in group COC (p=0.521). The intensity of migraine attacks was significantly different between baseline and 6-month treatment in group POP (p<0.001) but not in group COC (p=0.078). CONCLUSIONS: POP is better tolerated than COC and it seems to ameliorate migraine attacks compared to COC in symptomatic patients with rectovaginal endometriosis and migraine without aura. Both drugs efficaciously relieve endometriosis-related pain symptoms. This study supports the use of the POP in women with rectovaginal endometriosis and coexisting migraine without aura.

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Westling, A. M., Tu, F. F., Griffith, J. W. and Hellman, K. M. 2013.

The association of dysmenorrhea with noncyclic pelvic pain accounting for psychological factors. Am J Obstet Gynecol.

OBJECTIVE: The factors that underlie pelvic pain are poorly understood. Specifically, the relative influence of dysmenorrhea and psychological factors in the etiology of noncyclic pelvic pain conditions, such as interstitial cystitis and irritable bowel syndrome, is unknown. To further characterize pelvic pain, we compared the frequency of menstrual, somatosensory, and psychological risk factors between women with and without severe noncyclic pelvic pain symptoms. **STUDY DESIGN:** A total of 1012 reproductive-aged women completed a 112-item questionnaire with domains including mood, fatigue, physical activity, somatic complaint, and pain. Questionnaire items included existing items for menstrual distress and newly written items derived from qualitative interviews. The relationship of dysmenorrhea and noncyclic pelvic pain complaints (dyspareunia, dyschezia, or dysuria) was modeled using quantile regression. **RESULTS:** Among women who menstruate regularly, those with dysmenorrhea had disproportionately more severe noncyclic pelvic pain (54/402, 13%) than women without dysmenorrhea (5/432, 1%; odds ratio, 13; 95% confidence interval, 5-33). In a multivariate-adjusted model, dysmenorrhea ($\beta = .17$), activity capability ($\beta = .17$), somatic complaint ($\beta = .17$), and bodily pain ($\beta = .12$) were the primary predictors of noncyclic pelvic pain. Depression ($\beta = .03$) and anxiety ($\beta = .01$) were not significantly predictive. The presence of dysmenorrhea, somatic complaint, and low activity capability predicted 90% of the cases of women with noncyclic pelvic pain. **CONCLUSION:** The association between dysmenorrhea and noncyclic pelvic pain suggests that menstrual pain is an etiological factor in noncyclic pelvic pain, whereas depression and anxiety may be secondary effects. Longitudinal studies are needed to determine whether dysmenorrhea causally influences development of noncyclic pelvic pain or shares common underlying neural mechanisms.

Appendix E. Summary Table

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
|---|--|---------------------------------------|---|-------------------------|
| Key Question 1: Prevalence and Comorbidities | | | | |
| Noncyclic CPP was variably defined, and diagnostic approaches were rarely reported. [Key finding] | No new studies were identified | No new literature was identified | Two reviewers felt that the conclusions in the original CER were current, and two were unsure. One reviewer noted that the field's understanding of CPP is changing, with a recognition that patients with CPP may represent a heterogeneous group with dysfunction in various organ systems, including the central nervous system. The same reviewer suggested that additional evidence may be found in literature related to interstitial cystitis, painful bladder syndrome, and vulvodynia, as these conditions, as well as fibromyalgia, as CPP is now suspected to be more common in women with these conditions. No specific studies were suggested. A second reviewer noted that MAPP research network studies of painful bladder and irritable bowel syndrome and related CPP were not included. This reviewer | Likely current |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| | | | suggested 12 studies ¹⁻¹² of the MAPP Research Network that did not meet population inclusion criteria. The same reviewer also suggested three additional studies ¹³⁻¹⁵ examining prevalence/comorbidities that also did not meet population inclusion criteria. | |
| Disproportionately few studies addressed noncyclic CPP, given the prevalence of the condition. [Key finding] | No new studies were identified | No new literature was identified | See above | Likely current |
| Comorbidities were similarly variably defined and frequently not diagnosed using standardized criteria. [Key finding] | No new studies were identified | No new literature was identified | See above | Likely current |
| Dysmenorrhea, dyspareunia, and IBS were the most frequently reported comorbidities in the literature meeting our criteria. [Key finding] | No new studies were identified | A cross sectional study found that Among women who menstruate regularly, those with dysmenorrhea had disproportionately more severe noncyclic pelvic pain (54/402, 13%) than women without dysmenorrhea (5/432, 1%; odds ratio, 13; 95% confidence interval, 5-33). In a multivariate-adjusted model, dysmenorrhea (beta = .17), activity capability (beta = .17), somatic complaint | See above | Likely current |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| | | <p>(beta = .17), and bodily pain (beta = .12) were the primary predictors of noncyclic pelvic pain. Depression (beta = .03) and anxiety (beta = .01) were not significantly predictive. The presence of dysmenorrhea, somatic complaint, and low activity capability predicted 90% of the cases of women with noncyclic pelvic pain.</p> <p>One prospective cohort study found that women with deep endometriosis related pain (dysmenorrhea, pelvic pain, dyspareunia) showed the highest level of perceived stress.</p> | | |
| Key Question 2. Outcomes of Surgical Interventions for CPP | | | | |
| Intervention studies overall included a limited number of participants and typically included only short-term followup. | No new studies were identified | | One reviewer believed the original CER conclusions to be current, one felt that some of them were supported, and the other two reviewers were unsure. One reviewer suggested small studies of the effect of surgical excision and rectovaginal endometriosis. The same reviewer also suggested literature related to pelvic congestion syndrome therapies, and | Likely current |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| | | | <p>excision for severe adhesions. No specific studies were suggested. A third reviewer suggested including studies related to surgery (e.g., laser comparison studies), and suggested five studies. One study¹⁶ did not meet inclusion criteria for outcomes, and one study¹⁷ was already included that did not meet population inclusion criteria due to primary diagnoses of endometriosis.</p> <p>Included studies:</p> <p>In one study¹³ (Ruffo et al., 2014; n=774), a long term follow up after laparoscopic bowel resections for deep infiltrating endometriosis, patients reported significant improvement in chronic pelvic pain, as well as well as dyspareunia, constipation (p=.0001), and constipation (p=.004) over an average of 54 months.</p> <p>An RCT¹⁴ (Seracchioli et al., 2014; n=80) found no differences in post-surgery pelvic pain when</p> | |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| | | | <p>comparing ovarian suspension in endometriosis surgery to control.</p> <p>A prospective cohort study¹⁵ (Meuleman et al., 2014; n=200) compared women with deeply infiltrative endometriosis undergoing CO2 laser ablative surgery with and without bowel resection, and found significant improvement in quality of life and visual analogue scales up to two years after surgery, with no difference between groups.</p> | |
| Few studies of surgical approaches examined the same approach; none used a placebo control. [Key finding] | No new studies were identified | No new literature was identified | See above | Likely current |
| No surgical approach was superior to a nonsurgical approach or comparative surgical approach. [Key finding] | No new studies were identified | No new literature was identified | See above | Likely current |
| The strength of the evidence for surgical approaches overall was insufficient to low. [Key finding] | No new studies were identified | No new literature was identified | See above | Likely current |
| Among studies addressing treatment effects, little evidence demonstrates the effectiveness of surgical approaches. Despite numerous surgical techniques | No new studies were identified | One prospective cohort study ¹⁷ (Lazzeri et al., 2015) found that after surgery for endometriosis, perceived stress significantly | See above | Likely current |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| used extensively in treating CPP, few studies included more than 50 participants, and few were considered high quality. All of the studies with comparison data failed to demonstrate that surgery in general or any specific surgical technique was more efficacious than either nonsurgical intervention or the comparator technique in improving pain status in patients. No surgical technique was superior, and the evidence to conclude that surgical intervention is either effective or ineffective for the treatment of CPP is insufficient. [Conclusion] | | decreased. | | |
| Intervention studies overall included a limited number of participants and typically included only short-term followup. [Key finding] | No new studies were identified | No new literature was identified | See above | May not be current due to two studies with longer term follow up identified (54 mo; 24 mo). |
| Key Question 3: Evidence for Differences in Surgical Outcomes by Etiology | | | | |
| No studies addressed evidence for differences in outcomes by etiology. [Key finding] | No new studies were identified | No new literature was identified | Two reviewers felt that the original CER conclusions were still current, one was unsure, and the fourth felt that no study design could adequately address the key question. One reviewer suggested small studies of the effect of surgical excision and rectovaginal | Likely current |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| | | | endometriosis. No specific studies were suggested. | |
| Key Question 4: Outcomes of Nonsurgical Interventions for CPP | | | | |
| Most studies of nonsurgical approaches meeting our criteria addressed hormonal approaches and included women with endometriosis-associated CPP. [Key finding] | No new studies were identified | No new literature was identified | Two reviewers felt that the conclusions in the original CER were still current, one reviewer felt that studies of levonorgestrel IUD were missing as it is commonly used in clinical practice, and the fourth reviewer felt that studies of non-surgical non-hormonal interventions were missing. | Likely current |
| Few studies of nonsurgical interventions were placebo controlled, and few addressed nonpharmacologic approaches; strength of evidence was insufficient to low. [Key finding] | Two new RCTs were identified: one RCT (N= 61) using micronized NPalmityolethanolamine transpolydatin or Celecoxib to treat CPP related to endometriosis after laparoscopic assessment reported a decrease in dysmenorrhea, dyspareunia, and pelvic pain with both agents compared to placebo, Celecoxib was most effective; the other RCT (N=59) concluded that the administration of antioxidants reduces chronic pelvic pain compared to placebo in women with endometriosis and chronic pelvic pain. | A systematic review ¹⁸ (Cheong et al., 2015) found that the estimated effect of lofexidine on pain outcomes when compared with placebo was compatible with benefit and harm (Peto OR 0.42, 95% CI 0.11 to 1.61, one study, 39 women, low-quality evidence). Women in the lofexidine group reported more adverse effects (including drowsiness and dry mouth) than women given placebo (moderate-quality evidence). Head-to-head comparisons showed that women taking goserelin had greater improvement in pelvic pain score (MD 3, | One reviewer indicated that the systematic review identified in the SRC literature search indicates that transvenous occlusion may be a beneficial approach. | Likely current (studies of lofexidine, and goserelin vs. progestogen included in Cheong et al. ¹⁸ , were excluded from the original systematic review due to sample size). |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| | | 95% CI 2.08 to 3.92, one study, n = 47, moderate-quality evidence) at one year than those taking progestogen. Women taking gabapentin had a lower VAS pain score than those taking amitriptyline (MD - 1.50, 95% CI -2.06 to -0.94, n = 40, low-quality evidence). Study authors reported that no statistically significant difference was observed in the rate of adverse effects among women taking gabapentin compared with women given amitriptyline. | | |
| Hormonal studies reported equal effectiveness among the active agents investigated, with the exception of a placebo-controlled trial of raloxifene reporting more rapid return of pain in the raloxifene group. [Key finding] | No new studies were identified | A systematic review ¹⁸ (Cheong et al., 2015) found two studies reporting that progestogen was more effective than placebo in women achieving > 50% reduction in visual analogue scale pain score immediately after treatment (Peto OR 3.00, 95% CI 1.70 to 5.31, two studies, n = 204, I(2) = 22%, moderate-quality evidence). Evidence of benefit was maintained up to nine months after treatment (Peto OR 2.09, 95% CI 1.18 to 3.71, two | See above | Likely current |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| | | <p>studies, $n = 204$, $I(2) = 0\%$, moderate-quality evidence). Women treated with progestogen reported more adverse effects (e.g. weight gain, bloating) than those given placebo (high-quality evidence).</p> <p>A patient preference trial¹⁹ (Morotti et al., 2014) comparing a progestogen only contraceptive pill to a combined contraceptive in women with pain related to endometriosis and migraines found similar reductions in chronic pelvic pain and dyspareunia over 6-months in both groups, with a larger percentage of patient reporting satisfaction in the progestogen only group (61.2% vs. 37.8%), as well as a significant reduction in the number of migraines ($p=.002$). No reduction of migraines were found in the combined group.</p> | | |
| Studies of nonhormonal and nonpharmacologic agents reported some positive effects on pain status. [Key finding] | | A systematic review ¹⁸ (Cheong et al., 2015) found that women who underwent reassurance ultrasound scans and received counseling were more likely | One reviewer noted that there were no studies of interventions other than hormonal agents included in the original report, and stated that there is evidence | May not be current due one systematic review of transvenous occlusion. |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| | | <p>to report improved pain than those treated with a standard 'wait and see' policy (Peto OR 6.77, 95% CI 2.83 to 16.19, n = 90, low-quality evidence). Significantly more women who had writing therapy as a disclosure reported improvement in pain than those in the non-disclosure group (Peto OR 4.47, 95% CI 1.41 to 14.13, n = 48, very low-quality evidence). No difference between groups in pain outcomes was noted when other psychological therapies were compared with standard care or placebo (quality of evidence ranged from very low to low).</p> <p>One systematic review²¹ (Hansrani et al., 2015), of thirteen studies including 866 women undergoing trans-venous occlusion of pelvic veins for CPP found statistically significant improvements in pelvic pain were reported in nine of the 13 studies. Technical success was reported in 865 of 866 (99.8%) with low complication rates: coil migration in 14 women</p> | <p>regarding other approaches being studied in other disciplines. This reviewer suggested the MAPP research network studies, as well as studies of interventions such as myofascial and specific pain therapies. None of the 12 suggested MAPP studies¹⁻¹² met population inclusion criteria. The same reviewer also suggested one retrospective chart review²⁰ of transvaginal pelvic floor physical therapy that did not meet study design inclusion criteria.</p> | |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| | | (1.6%), abdominal pain in ten women (1.2%) and vein perforation in five (0.6%). In a study on varicose veins of the legs, recurrence was seen in 13% of 179 women 5-years following coil embolization. Subjective improvements in pain were seen in all 13 studies after treatment by trans-venous occlusion. All 13 studies were of poor methodological quality. Complication rates were low and no fatalities occurred. | | |
| Few nonsurgical studies reported harms. [Key finding] | One of the two new RCTs reported on side effects (no significant effects or alterations of laboratory data). | A systematic review ¹⁸ (Cheong et al., 2015) identified no studies of psychological treatments that reported adverse events. | Reviewers had no comment. | Likely current |
| Studies of nonsurgical approaches typically addressed hormonal management of endometriosis-related CPP and were not placebo controlled, thus limiting our ability to understand whether hormonal therapies would be beneficial for women with CPP without endometriosis and whether pain relief reported is due simply to the placebo effect. Some studies reported benefits of other nonsurgical | The two new RCTs addressed non-hormonal interventions and both were placebo controlled but both were in endometriosis-related CPP. | No new literature was identified | One reviewer suggested examining studies related to the use of levonorgestrel IUD for CPP related to dysmenorrhea and CPP related to endometriosis, as it is now commonly used in clinical practice, and the reviewer believed that several trials found a reduction in CPP. No specific studies were suggested. | Likely current |

| Conclusions From CER Executive Summary | Literature Analysis from Most Recent Surveillance Assessment (Oct 2012 – Link to Paper) | Current Literature Search (July 2015) | Expert Opinion | Surveillance Assessment |
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| approaches, but nonhormonal and nonpharmacologic management remains understudied. [Conclusions] | | | | |
| Key Question 5: Evidence for Selecting One Intervention Over Another | | | | |
| No studies addressed [...] evidence for selecting one intervention over another if an intervention failed. [Key finding] | The conclusions are still valid. | No new literature was identified | One reviewer suggested examining studies related to the use of levonorgestrel IUD, as well as studies related to fibromyalgia, migraines, and irritable bowel syndrome. | Likely current |

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