Draft Comparative Effectiveness Review

Number XX

Noncyclic Chronic Pelvic Pain Therapies for Women

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

This information is distributed solely for the purposes of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the Agency for Healthcare Research and Quality. It does not represent and should not be construed to represent an Agency for Healthcare Research and Quality or Department of Health and Human Services determination or policy.

Contract No.

Prepared by:

Investigators

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials noted, for which further reproduction is prohibited without the specific permission of copyright holders.

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

Suggested Citation:
[Authors]. Comparative Effectiveness of Therapies for Noncyclic Chronic Pelvic Pain in Women. Comparative Effectiveness Review No. [#]. (Prepared by the XXX Evidence based Practice Center under Contract No. [#].) Rockville, MD: Agency for Healthcare Research and Quality. [Month Year]. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm

This report is based on research conducted by the XXX Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. XXXX). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director, Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Shilpa Amin, M.D., MBsc, F.A.A.F.P.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Acknowledgments

Key Informants

Technical Expert Panel

Peer Reviewers

EPC Program Director

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Agency for Healthcare Research and Quality

AHRQ Contacts

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Shilpa Amin, M.D., MBsc, F.A.A.F.P.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Structured Abstract

Objectives: We systematically reviewed evidence on therapies for women over age 18 with noncyclic chronic pelvic pain (CPP). We focused on the prevalence of conditions thought to occur commonly with CPP; changes in pain, functional status, quality of life, and patient satisfaction resulting from surgical and nonsurgical treatment approaches; harms of nonsurgical approaches; evidence for differences in surgical outcomes if an etiology for CPP is identified post-surgery; and evidence for selecting one intervention over another after an approach fails.

Data Sources: We searched MEDLINE® via PubMed, PsycInfo®, EMBASE Drugs and Pharmacology, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases as well as the reference lists of included studies.

Review Methods: We included studies published in English from January 1990 to January 2011. We excluded intervention studies with fewer than 50 adult women with CPP; cross-sectional studies or case series with fewer than 100 women with CPP addressing the prevalence of comorbidities; and studies lacking relevance to CPP treatment.

Results: Of 33 included studies, 17 were randomized controlled trials (RCTs) (2 good, 3 fair, and 12 poor quality), 3 were cohort studies or nonrandomized trials (3 poor quality), and 13 were cross-sectional studies addressing the prevalence of comorbidities (quality varied by comorbidity). The most frequently reported comorbidities were dysmenorrhea, dyspareunia, and irritable bowel syndrome (IBS). Among studies addressing surgical interventions, there was no evidence that laparoscopic utero-sacral nerve ablation (LUNA) is more effective than simple diagnostic laparoscopy and no evidence of benefit of lysis of adhesions. Evidence was insufficient to comment on relief of pain after hysterectomy. Eight studies of nonsurgical approaches assessed hormonal therapies for endometriosis-associated CPP and reported similar effectiveness among active agents. One exception was an RCT comparing raloxifene with placebo, which reported more rapid return of pain in the raloxifene group. Few studies assessed nonhormonal medical or nonpharmacologic management; benefits were reported in single studies of a pelvic physiotherapy approach, botulinum toxin, pelvic ultrasonography, and an integrated management approach. No studies provided evidence relating to a trajectory of care. Reporting of harms data was very limited.

Conclusions: Improved characterization of the targeted condition, intervention, and population in CPP research is necessary to inform treatment choices for this commonly reported entity. A uniform definition of CPP and standardized evaluation of participants are lacking across the literature. Study populations likely vary widely, and studies may be reporting effects from treating symptoms rather than a diagnosed condition. Thus our understanding of potential treatment effects is diluted. Similarly, understanding comorbidity prevalence with CPP is difficult as conditions may be considered part of the differential diagnosis or a concomitant condition. Among studies addressing treatment effects, little evidence demonstrates the effectiveness of surgical approaches. 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 is due simply to the placebo effect. Some studies reported benefits of other nonsurgical approaches, but nonhormonal and nonpharmacologic management remain understudied.

Contents

Executive Summary ES-1

Introduction 1
Overview 1
Prevalence 1
Health Impact 1
Etiology 2
Comorbidities 2
Evaluation of CPP 3
Interventions 3
Summary 4
Scope and Key Questions 4
Scope of the Report 4
Key Questions 4
Organization of This Evidence Report 5
Uses of This Report 5

Methods 7
Topic Development and Refinement 7
Analytic Framework 7
Literature Search Strategy 8
Process for Study Selection 9
Data Extraction and Data Management 12
Individual Study Quality Assessment 12
Randomized Controlled Trials 13
Observational Studies 14
Studies Addressing the Prevalence of Comorbidities of Interest 17
Determining Quality Levels 18
Data Synthesis 19
Grading the Body of Evidence for Each Key Question 19
Peer Review and Public Commentary ..... <To be added>

Results 21
Article Selection 21
KQ1. Among women who have been diagnosed with noncyclic/mixed cyclic and noncyclic CPP, what is the prevalence of comorbidities of interest? .. 24

Overview of the Literature 24
Key Points 25
Detailed Analysis 25
KQ2. 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? 32
Overview of the Literature 33
Key Points 33
Detailed Analysis 33
KQ3. What is the evidence that surgical outcomes differ if the etiology of noncyclic/mixed cyclic and noncyclic CPP is identified after surgery? 38
KQ4. 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? 38
Overview of the Literature 38
Key Points 39
Detailed Analysis 39
KQ5. 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)? 47

Summary and Discussion 49
State of the Literature 49
Summary of Outcomes by Key Question 50
Strength of the Evidence for Effectiveness of Therapies 51
Overview 51
Strength of the Evidence by Key Question 51
Applicability 58
Applicability of the Evidence for Surgical Approaches 61
Applicability of the Evidence for Nonsurgical Approaches 62
Future Research 63
Gaps in Areas of Research 63
Methodologic Issues 67
Conclusions 68

References 70

Acronyms and Abbreviations 75

Figures

Figure ES1. Analytic Framework ES-3
Figure ES2. Literature Flow Diagram ES-5
Figure 1. Analytic Framework 8
Figure 2. Disposition of Articles Located for Review 22

Tables

Table 1. Inclusion and Exclusion Criteria 9
Table 2. Description of Study Quality Levels 18
Table 3. Overview of Noncyclic CPP Literature Addressing the Prevalence of Comorbidities of Interest 23
Table 4. Overview of Noncyclic CPP Literature Addressing Treatment Approaches 23
Table 5. Prevalence of Back Pain in Women with Noncyclic CPP 25
Table 6. Prevalence of Dysmenorrhea in Women with Noncyclic CPP 27
Table 7. Prevalence of Dyspareunia in Women with Noncyclic CPP 28
Table 8. Prevalence of Irritable Bowel Syndrome in Women with Noncyclic CPP 31
Table 9. Key Outcomes of Surgical Interventions for Noncyclic CPP 36
Table 10. Key Outcomes of Hormonal Therapies for Noncyclic CPP 40
Table 11. Key Outcomes of Nonhormonal Pharmacologic Treatments for Noncyclic CPP 43
Table 12. Key Outcomes of Nonpharmacologic Treatment for Noncyclic CPP 44
Table 13. Key Outcomes of Studies Comparing Nonsurgical With Surgical Treatment for Noncyclic CPP 46
Table 14. Nonsurgical Harms Reported in Placebo-Controlled Studies 46
Table 15. Summary of Results and Strength of Evidence of Studies Assessing Surgical Interventions 52
Table 16. Strength of Evidence Domains for Studies Assessing Surgical Interventions 53
Table 17. Summary of Results and Strength of Evidence of Studies Assessing Nonsurgical Interventions 55
Table 18. Strength of Evidence Domains for Studies Assessing Nonsurgical Interventions 56
Table 19. Summary of Outcome Measures 58
Table 20. Applicability of the Noncyclic CPP Evidence 61
Table 21. Descriptions/Definitions of CPP in Studies Assessed 64

Appendixes

Appendix A: Search Strategy
Appendix B: List of Excluded Studies
Appendix C: Evidence Tables
Appendix D: Data Extraction Forms
Appendix E: Quality of the Literature
Appendix F: Applicability Tables

Appendixes cited in this report are available at http://ahrq.gov/XXXXX **[AHRQ will supply the rest of the information for this statement.]**

Effective Health Care

Comparative Effectiveness of Therapies for Women with Noncyclic Chronic Pelvic Pain

Executive Summary

Effective Health Care Program

The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

Chronic pelvic pain in women is a commonly occurring and poorly understood condition. Little consensus on the definition of the condition exists—the duration of pelvic pain considered chronic in published studies varies from 3 to more than 6 months, and the location and pathology of the pain are largely unspecified.[1] The American College of Obstetricians and Gynecologists defines chronic pelvic pain as "noncyclical pain of at least 6 months' duration that appears in locations such as the pelvis, anterior abdominal wall, lower back, or buttocks, and that is serious enough to cause disability or lead to medical care"[2]. Noncyclic chronic pelvic pain (CPP) is the focus of this review. Noncyclic CPP excludes chronic pelvic pain that is limited to dysmenorrhea (pain with menstruation), or dyspareunia (pain with intercourse), dyschezia (pain with bowel movement), or dysuria (pain with urination).[3, 4] Noncyclic CPP is sometimes described simply as "chronic pelvic pain" in the literature because many subdivide chronic pelvic pain into dysmenorrhea, dyspareunia, and nonmenstrual CPP.[2]

For this review, we defined noncyclic CPP as pain that has persisted for more than 3 months, is localized to the anatomic pelvis (lower abdomen below the umbilicus), and is of sufficient severity that it causes the patient to become functionally disabled or to seek medical care. CPP as described throughout this review refers to noncyclic or mixed cyclic/noncyclic pelvic pain unless otherwise noted.

The causes of CPP are not well understood and may be associated with gynecologic (e.g., endometriosis) and nongynecologic (e.g., irritable bowel syndrome [IBS]) conditions. Diagnosis of an underlying cause is complicated because the pain is rarely associated with a single underlying disorder or contributing factor;[5] Howard outlined more than 60 diseases and conditions associated with CPP.[5]Frequently diagnosed etiologies include endometriosis,

adhesions, IBS, and interstitial cystitis (IC)/painful bladder syndrome (PBS);[6] however, a definitive diagnosis is often not made.

Objectives

Population. We focused this review on women over the age of 18 with noncyclic or mixed cyclic/noncyclic chronic pelvic pain. Throughout this review, CPP refers to noncyclic or mixed cyclic/noncyclic pelvic pain unless otherwise noted.

Interventions. Interventions included surgical approaches such as hysterectomy and laparoscopy and nonsurgical approaches including medical management and integrative interventions.

Comparators. Comparators included no treatment, placebo, or comparative interventions or combinations of interventions.

Outcomes. Our outcomes of interest included:

- Pain status (reduction in pain, pain recurrence, subsequent intervention for unresolved or worsening pain);
- Functional status (activities of daily living, sexual functioning);
- Quality of life;
- Patient satisfaction with pain management; and
- Harms or adverse effects of nonsurgical interventions.

Key Questions

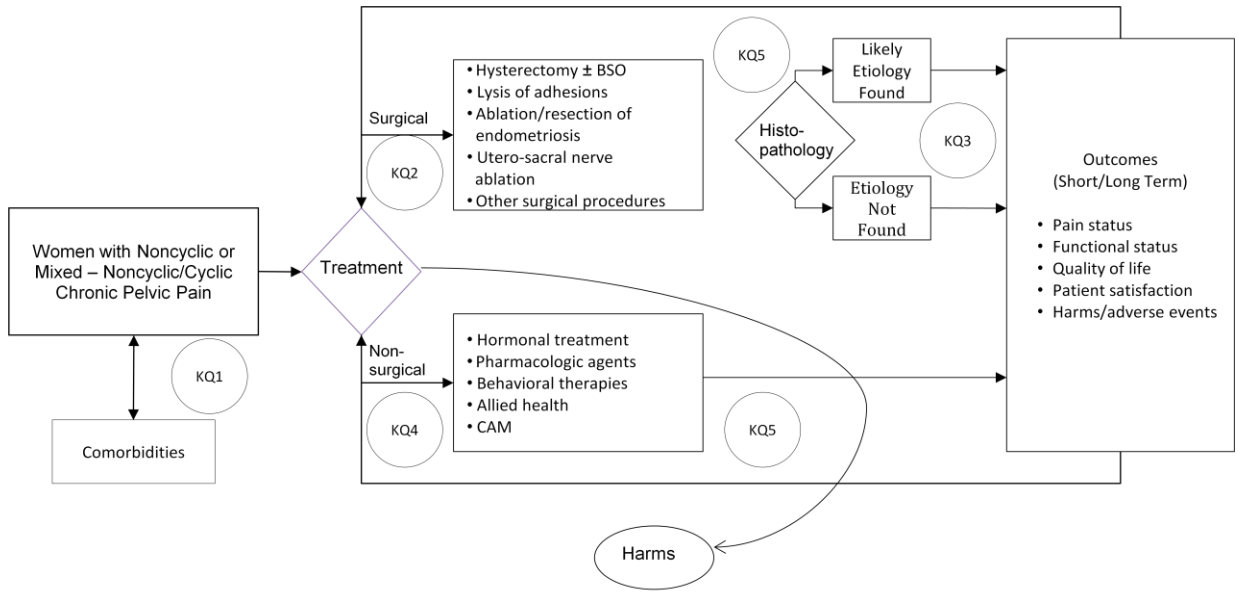
Key questions (KQ) were:

KQ1: 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?
KQ2: 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?
KQ3: What is the evidence that surgical outcomes differ if the etiology of noncyclic/mixed cyclic and noncyclic CPP is identified after surgery?
KQ4: 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?
KQ5: 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)?

Analytic Framework

We developed the analytic framework (Figure 1) based on clinical expertise and refined it with input from our key informants and Technical Expert Panel (TEP) members. The framework summarizes the process by which women with CPP make and modify treatment choices. Treatment choices include surgical or nonsurgical approaches and may lead to outcomes including changes in pain status (e.g., resolution of pain, continuing pain, continued need for pain medication), patient satisfaction, quality of life, or harms/adverse effects. In addition, outcomes may vary by diagnosis in those patients receiving a confirmed diagnosis for the etiology of their CPP.

Figure ES-1. Analytic framework for therapies for women with CPP



BSO=bilateral salpingo-oopherectomy; CAM=complementary and alternative medicine; KQ=Key Question

Methods

Input from Stakeholders

The topic was nominated in a public process. With key informant input, we drafted initial key questions and, after review by the Agency for Healthcare Research and Quality (AHRQ), they were posted to a public website for public comment. Using public input, we drafted final key questions, which were approved by AHRQ. We convened a TEP to provide input during the project on issues such as setting inclusion/exclusion criteria and assessing study quality. In addition, the draft report was peer reviewed and available for public comment.

Data Sources and Selection

We searched 4 databases: MEDLINE® via the PubMed interface, PsycINFO (psychology and psychiatry literature), EMBASE Drugs and Pharmacology, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) database. We hand searched reference lists of included articles and recent reviews for additional studies. We excluded studies that:

- did not include women over the age of 18 with noncyclic CPP;
- did not report information pertinent to the key questions;
- were primarily focused on coexisting conditions, cancer pain, or pregnancy-related pain;
- were not published in English;
- were published prior to the year 1990;
- were not original research;
- were retrospective studies or case series (unless they included ≥100 participants and reported harms or comorbidity data).

We also excluded studies with fewer than 50 total participants for studies assessing the effects of surgical or nonsurgical interventions; addressing difference in surgical outcomes by etiology; or presenting evidence for selecting one intervention over another.

We accepted controlled trials and prospective cohort studies with at least 50 participants with CPP and case series and cross-sectional studies with at least 100 participants with CPP and addressing harms or the prevalence of comorbidities identified in KQ1. Two reviewers separately evaluated each abstract. If one reviewer concluded that the article could be eligible, we retained it. Two reviewers independently read the full text of each included article to determine eligibility, with disagreements resolved via third-party adjudication.

Data Extraction and Quality Assessment

Data extraction. All team members entered information into the evidence tables. After initial data extraction, a second team member edited entries for accuracy, completeness, and consistency. In addition to outcomes for treatment effectiveness, we extracted data on harms/adverse effects.

Quality assessment. Two reviewers independently assessed quality with differences resolved though discussion, review of the publications, and consensus with the team. We rated studies as good, fair, or poor quality and retained poor studies as part of the evidence base discussed in this review. More information about our quality assessment methods is in the full report.

Data Synthesis and Analysis

Evidence synthesis. We used summary tables to synthesize studies that included comparison groups and summarized the results qualitatively.

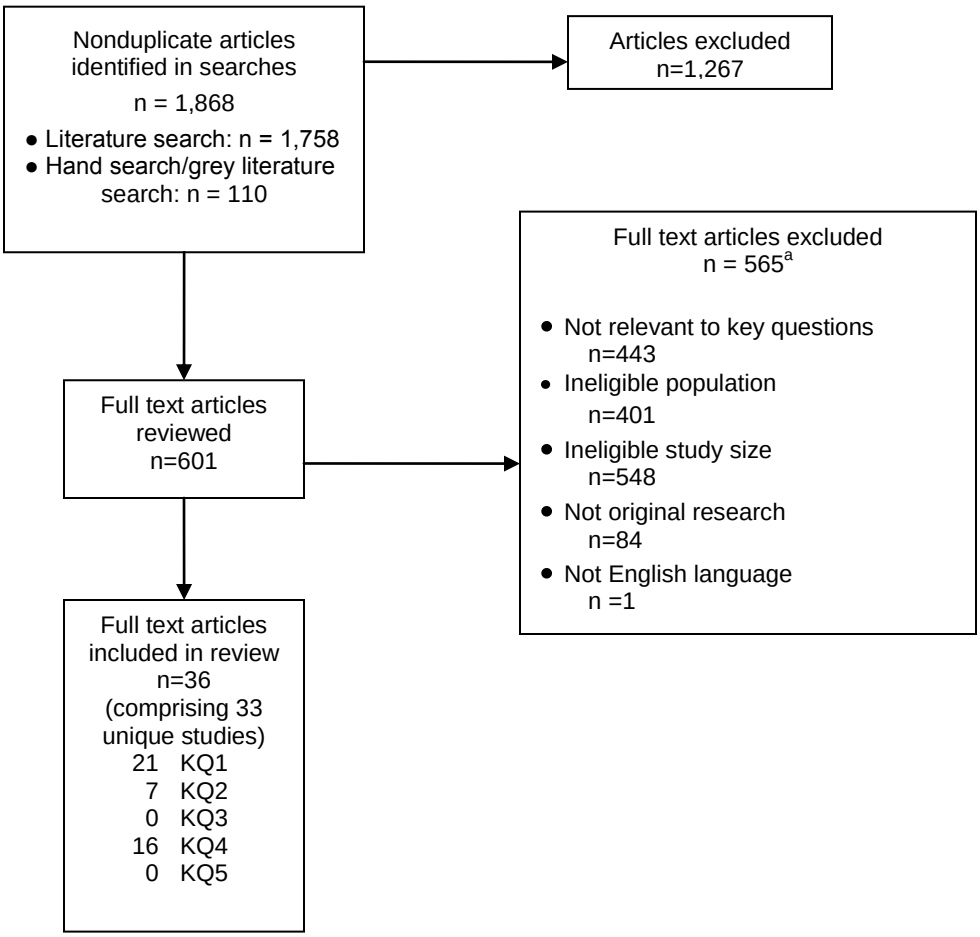
Strength of evidence. The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence. Strength of evidence can be regarded as insufficient, low, moderate, or high. It describes the adequacy of the current research, in quantity and quality, and the degree to which the entire body of current research provides a consistent and precise estimate of effect. We established methods for assessing the strength of evidence based

on the Evidence-based Practice Centers' (EPC) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[7]

Results

Our searches retrieved 1,868 nonduplicate citations. We reviewed the full text of 601 articles and included 36 articles, comprising 33 unique studies, in the full review. The full report details reasons for exclusion.

Figure ES-2. Disposition of articles located for the review



[a]The total number of articles in the exclusion categories exceeds the number of articles excluded because most of the articles fit into multiple exclusion categories; KQ=key question; n=number

KQ1: Prevalence of Comorbidities

We identified 21 unique studies addressing the prevalence of comorbidities of interest for this review.[8-31] Dyspareunia (11 studies), dysmenorrhea (9 studies), and IBS (8 studies) were the most frequently reported comorbidities in women with CPP with rates ranging from 15 to 88 percent, 13 to 100 percent, and 24 to 39 percent, respectively. Rates for other comorbidities also varied widely, and studies were largely of poor quality. Studies frequently failed to use validated diagnostic criteria and may not have provided an operational definition for a given comorbidity. We did not assess the strength of evidence for studies addressing this key question as we were interested in data regarding the prevalence of comorbid conditions and not effectiveness of interventions.

KQ2: Outcomes of Surgical Interventions for CPP

We located 7 unique studies addressing surgical interventions for CPP, 5 randomized controlled trials (RCTs)[9, 13, 32-34] and 2 prospective cohort studies.[16, 35] One good quality RCT evaluated laparoscopic lysis of intraabdominal adhesions[32] and reported no improvement in pain scores over diagnostic laparoscopy. Similarly, no studies reported benefit of laparoscopic utero-sacral nerve ablation (LUNA) compared with simple diagnostic laparoscopy. One poor quality study evaluated hysterectomy for CPP pain relief compared with nonsurgical management and reported greater patient satisfaction in the hysterectomy group, though data for women with noncyclic CPP alone are difficult to isolate. We assessed the strength of evidence for all surgical interventions except LUNA as insufficient. With 2 RCTs, one of fair[33] and one of poor quality,[9] we considered the strength of evidence to be low for the lack of efficacy of LUNA to improve pain status over diagnostic laparoscopy alone.

KQ3: Evidence for Differences in Surgical Outcomes by Etiology

We did not locate any studies addressing this question.

KQ4: Outcomes of Nonsurgical Interventions for CPP

We located 16 unique studies addressing nonsurgical interventions.[8, 10-16, 35-43] Only one study was rated as good quality,[14, 15] 3 were fair quality,[10, 36, 37] and the balance were poor.[8, 11-13, 16, 35, 38-42.]

Eight studies addressed hormonal treatments for endometriosis-associated CPP and reported equal effectiveness among active agents investigated, with the exception of a placebo-controlled trial of raloxifene. This RCT reported more rapid return of pain in the raloxifene group, and the trial was stopped early.[14] The few (n=3) placebo-controlled studies were of fair or good quality and reported larger size of effect (60 to 70 percent range) than studies comparing 2 active agents. RCTs of botulinum toxin[36] and gabapentin and amitriptyline or either agent alone[8] reported some improvements in pain scores. Few studies addressed nonhormonal or nonpharmacologic management: one fair quality RCT of a pelvic physiotherapy technique reported improvement in pain scores in the treatment group; one poor quality study reported no benefit from post-operative counseling augmented with displaying operative photographs while discussing findings with participants; and two poor quality trials reported some benefits from an integrated treatment approach and ultrasonography plus counseling. Reporting of harms data was very limited among

trials; among the placebo-controlled trials, harms were more frequent in the placebo arms. We assessed the strength of evidence for all nonsurgical interventions as insufficient.

KQ5: Evidence for Selecting one Intervention Over Another

We did not locate any studies addressing this question.

Discussion

Key findings

The prevalence rates for the comorbidities we examined showed significant variation. Frequently no operational definition or diagnostic criteria for comorbidities were provided. When definitions or criteria were available, they were rarely consistent across studies. Diagnostic methods varied and included patient report of symptoms, patient report that they were given the diagnosis by a health care provider, evaluation by a health care provider, and objective diagnostic criteria.

Given that many women with CPP are treated with invasive surgical procedures, remarkably little evidence exists that supports a surgical approach to the treatment of CPP. We identified and reviewed 2 articles comparing non-specific surgical approaches to nonsurgical approaches,[13, 16] one study addressing hysterectomy specifically,[35] one study evaluating laparoscopic adhesiolysis at the time of diagnostic laparoscopy,[32] 2 articles evaluating LUNA compared to diagnostic laparoscopy,[9, 33] and one paper directly comparing LUNA and utero-sacral ligament resection.[34]

In none of the studies with comparison data was surgery in general or any specific surgical technique better than either nonsurgical intervention or the comparator technique in improving pain status in patients. Given the limited number of studies addressing heterogeneous surgical interventions and so few of good or fair quality, it is difficult to summarize the evidence for the effect for surgical interventions on any of the outcomes proposed. Although no surgical technique emerged as a superior method for surgical intervention, the evidence is insufficient to conclude that surgical intervention is either effective or ineffective for the treatment of CPP

Studies of nonsurgical interventions were similarly subject to significant variation in study design and interventions addressed, which detracts from the ability to apply these study results to a broader population or provide concrete estimates for clinical effect. We saw this variation in 1) definition of pelvic pain, 2) patient populations, 3) outcome measures, 4) interventions, 5) timing of outcome measures and participant follow-up, and 6) comparators.

Only 3 of the 16 studies included in this section had a placebo arm for comparison. All of the other studies employed active treatments as comparators. This lack of placebo comparison detracts from the active head-to-head trials because no initial validation of effect has been made. It could easily be assumed that each active intervention works simply by placebo effect, and this could explain why each hormone-based treatment seems equally effective. Many studies also included a population of patients with endometriosis; few studies include participants with CPP due to another etiology. We found the evidence insufficient to assess the effectiveness of any nonsurgical therapies for CPP.

Applicability of Evidence

We set inclusion criteria intended to identify studies with applicability to women with noncyclic or mixed chronic pelvic pain. Studies differed considerably in terms of study populations, interventions, and outcome measures. Many of the studies were noncomparative.

Lack of direct comparisons of treatment options further hinders our ability to know what findings will best extend to a specific patient or to decisions about care protocols within clinics or health systems. Overall the data that are available have fair to good applicability to women with noncyclic/mixed CPP populations in settings within the United States though many studies were conducted in specialty treatment centers. In the nonsurgical literature, many studies included women with endometriosis-associated CPP.

Gaps in the Evidence and Methodologic Concerns

Despite a prevalence for noncyclic CPP rivaling that of widely studied conditions such as asthma,[44] little research assessing therapies exists. Whereas there are many publications regarding pelvic pain in general, there are relatively few addressing noncyclic CPP, and of those, few were evaluated as providing high quality evidence. Seventeen of 33 studies meeting our criteria were RCTs; however, only 3 were placebo controlled.[10, 14, 36] Some surgical studies compared a surgical approach to diagnostic laparoscopy or compared surgical to nonsurgical management. In the nonsurgical literature, most studies compared active agents to active agents, and a number addressed hormonal therapies for endometriosis-associated CPP.

The quality of those studies providing data about the prevalence of comorbidities varied by comorbidity, with the bulk of studies assessed as poor quality. Among studies reporting data on the prevalence of comorbidities, the range of prevalence estimates tended to be more narrow in those studies which employed validated diagnostic criteria (e.g., Rome criteria for IBS), and studies using validated criteria were of higher quality.

The literature overall is muddled by a lack of standardized definitions for CPP and unclear diagnostic evaluation that make it difficult to determine whether studies are truly including women with CPP. Systematic reviews of effectiveness of interventions for a symptom or syndrome are fraught with difficulty; the lack of specific diagnostic criteria results in heterogeneity within and across studies. In order to effectively treat any chronic pain, one would assume that a thorough diagnostic investigation would first take place. For many conditions, this typically follows some pre-determined algorithm. However, for CPP, no such algorithm exists. Thus, in each study (and likely for each individual practitioner), the patient is approached in a variable manner, and some possible diagnoses may or may not be ruled out before treatment begins. There is no assurance that the treated condition is the causative condition. Treating a symptom means that a study group will likely have a variety of etiologies – some may be amenable to the intervention under study, others may not. Compared to an intervention trial that follows established diagnostic criteria and targets an identified condition, dilution of potential benefits and harms may be occurring.

Future Research

Research addressing therapies for CPP is largely composed of trials of active agents or approaches with little placebo-controlled research and little evidence of thorough identification of patient characteristics and potential etiologies for CPP. Notably, we did not locate any studies providing evidence that surgical outcomes differ if the etiology CPP is identified after surgery

(KQ3). We did not locate any studies providing evidence for choosing one intervention over another to treat persistent or recurrent CPP after an initial intervention failed to achieve the target outcome(s) (KQ5). Future research needs include:

- Developing our understanding of the etiology of CPP including analysis of the distribution of underlying causes, including iatrogenic causes; identification of subgroups at risk of developing CPP; understanding of myofascial dysfunction and visceral hyperplasia in CPP; and assessing the effects of sex steroid hormone levels on pain perception
- Understanding the impact of CPP on heath care costs and resource utilization
- Standardizing terminology and definitions in CPP research and research investigating related comorbidities
- Formalizing and standardizing diagnostic approaches to promote clear delineation of patient populations in CPP research
- Standardizing outcome measures
- Investigating nonsurgical and nonpharmacologic approaches to CPP treatment including acupuncture, psychotherapy, cognitive behavioral therapy, and patient education
- Assessing nonhormonal pharmacologic therapies
- Comparing surgical and nonsurgical approaches in prospective studies
- Investigating the benefit of surgical approaches, including understanding patient populations likely to benefit, timing of intervention and potential therapeutic benefits of diagnostic laparoscopy
- Employing placebo controls and improving methodologic rigor in studies.

Conclusions

Improved characterization of the targeted condition, intervention, and population in CPP research is necessary to inform treatment choices for this commonly reported entity. A uniform definition of CPP and standardized evaluation of participants are lacking across the literature; study populations are likely vary widely, and studies may be reporting effects from treating symptoms rather than a diagnosed condition. Thus our understanding of potential treatment effects is diluted. Similarly, understanding comorbidity prevalence with CPP is difficult as conditions may be considered part of the differential diagnosis or a concomitant condition.

Among studies addressing treatment effects, little evidence demonstrates the effectiveness of surgical approaches. 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 remain understudied.

References

1. Williams RE, Hartmann KE and Steege JF. Documenting the current definitions of chronic pelvic pain: implications for research. Obstet Gynecol. 2004 Apr;103(4):686-91.

2. ACOG Practice Bulletin No. 51. Chronic pelvic pain. Obstet Gynecol. 2004 Mar;103(3):589-605

3. Stones W, Cheong Ying C, Howard Fred M, et al. Interventions for treating chronic pelvic pain in women. Journal [serial on the Internet]. 2005.

4. Leserman J, Zolnoun D, Meltzer-Brody S, et al. Identification of diagnostic subtypes of chronic pelvic pain and how subtypes differ in health status and trauma history. Am J Obstet Gynecol. 2006 Aug;195(2):554-60; discussion 560-1.

5. Howard FM. Chronic pelvic pain. Obstet Gynecol. 2003 Mar;101(3):594-611.

6. Howard Fred M. Evaluation of chronic pelvic pain in women. UpToDate. 2011(last updated April 9, 2010).

7. Owens DK, Lohr KN, Atkins D, et al. Grading the Strength of a Body of Evidence When Comparing Medical Interventions. 2008.

8. Sator-Katzenschlager SM, Scharbert G, Kress HG, et al. Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. Wien Klin Wochenschr. 2005 Nov;117(21-22):761-8.

9. Johnson NP, Farquhar CM, Crossley S, et al. A double-blind randomised controlled trial of laparoscopic uterine nerve ablation for women with chronic pelvic pain. BJOG. 2004 Sep;111(9):950-9.

10. Ling FW. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. Pelvic Pain Study Group. Obstet Gynecol. 1999 Jan;93(1):51-8.

11. Gestrinone versus a gonadotropin-releasing hormone agonist for the treatment of pelvic pain associated with endometriosis: a multicenter, randomized, double-blind study. Gestrinone Italian Study Group. Fertil Steril. 1996 Dec;66(6):911-9.

12. Vercellini P, Trespidi L, Colombo A, et al. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril. 1993 Jul;60(1):75-9.

13. Peters AA, van Dorst E, Jellis B, et al. A randomized clinical trial to compare two different approaches in women with chronic pelvic pain. Obstet Gynecol. 1991 May;77(5):740-4.

14. Stratton P, Sinaii N, Segars J, et al. Return of chronic pelvic pain from endometriosis after raloxifene treatment: a randomized controlled trial. Obstet Gynecol. 2008 Jan;111(1):88-96.

15. Karp BI, Sinaii N, Nieman LK, et al. Migraine in women with chronic pelvic pain with and without endometriosis. Fertil Steril. 2010 Dec 8.

16. Lamvu G, Williams R, Zolnoun D, et al. Long-term outcomes after surgical and nonsurgical management of chronic pelvic pain: one year after evaluation in a pelvic pain specialty clinic. Am J Obstet Gynecol. 2006 Aug;195(2):591-8; discussion 598-600.

17. Montenegro ML, Mateus-Vasconcelos EC, Rosa ESJC, et al. Postural changes in women with chronic pelvic pain: a case control study. BMC Musculoskelet Disord. 2009;10:82.

18. Pitts MK, Ferris JA, Smith AM, et al. Prevalence and correlates of three types of pelvic pain in a nationally representative sample of Australian women. Med J Aust. 2008 Aug 4;189(3):138-43.

19. Fenton BW, Durner C and Fanning J. Frequency and distribution of multiple diagnoses in chronic pelvic pain related to previous abuse or drug-seeking behavior. Gynecol Obstet Invest. 2008;65(4):247-51.

20. Paulson JD and Delgado M. The relationship between interstitial cystitis and endometriosis in patients with chronic pelvic pain. JSLS. 2007 Apr-Jun;11(2):175-81.

21. Verit FF, Verit A and Yeni E. The prevalence of sexual dysfunction and associated risk factors in women with chronic pelvic pain: a cross-sectional study. Arch Gynecol Obstet. 2006 Aug;274(5):297-302.

22. Tu FF, As-Sanie S and Steege JF. Prevalence of pelvic musculoskeletal disorders in a female chronic pelvic pain clinic. J Reprod Med. 2006 Mar;51(3):185-9.

23. Chung MH and Huh CY. Comparison of treatments for pelvic congestion syndrome. Tohoku J Exp Med. 2003 Nov;201(3):131-8.

24. Zondervan KT, Yudkin PL, Vessey MP, et al. Chronic pelvic pain in the community--symptoms, investigations, and diagnoses. Am J Obstet Gynecol. 2001 May;184(6):1149-55.

25. Bodden-Heidrich R, Kuppers V, Beckmann MW, et al. Psychosomatic aspects of vulvodynia. Comparison with the chronic pelvic pain syndrome. J Reprod Med. 1999 May;44(5):411-6.

26. Mathias SD, Kuppermann M, Liberman RF, et al. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. Obstet Gynecol. 1996 Mar;87(3):321-7.

27. Saravelos HG, Li TC and Cooke ID. An analysis of the outcome of microsurgical and laparoscopic adhesiolysis for chronic pelvic pain. Hum Reprod. 1995 Nov;10(11):2895-901.

28. Grace V and Zondervan K. Chronic pelvic pain in women in New Zealand: comparative well-being, comorbidity, and impact on work and other activities. Health Care Women Int. 2006 Aug;27(7):585-99.

29. Grace VM and Zondervan KT. Chronic pelvic pain in New Zealand: prevalence, pain severity, diagnoses and use of the health services. Aust N Z J Public Health. 2004 Aug;28(4):369-75.

30. Williams RE, Hartmann KE, Sandler RS, et al. Recognition and treatment of irritable bowel syndrome among women with chronic pelvic pain. Am J Obstet Gynecol. 2005 Mar;192(3):761-7.

31. Williams RE, Hartmann KE, Sandler RS, et al. Prevalence and characteristics of irritable bowel syndrome among women with chronic pelvic pain. Obstet Gynecol. 2004 Sep;104(3):452-8.

32. Swank DJ, Swank-Bordewijk SC, Hop WC, et al. Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-centre trial. Lancet. 2003 Apr 12;361(9365):1247-51.

33. Daniels J, Gray R, Hills RK, et al. Laparoscopic uterosacral nerve ablation for alleviating chronic pelvic pain: a randomized controlled trial. JAMA. 2009 Sep 2;302(9):955-61.

34. Palomba S, Russo T, Falbo A, et al. Laparoscopic uterine nerve ablation versus vaginal uterosacral ligament resection in postmenopausal women with intractable midline chronic pelvic pain: a randomized study. Eur J Obstet Gynecol Reprod Biol. 2006 Nov;129(1):84-91.

35. Carlson KJ, Miller BA and Fowler FJ, Jr. The Maine Women's Health Study: II. Outcomes of nonsurgical management of leiomyomas, abnormal bleeding, and chronic pelvic pain. Obstet Gynecol. 1994 Apr;83(4):566-72.

36. Abbott JA, Jarvis SK, Lyons SD, et al. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. Obstet Gynecol. 2006 Oct;108(4):915-23.

37. Heyman J, Ohrvik J and Leppert J. Distension of painful structures in the treatment for chronic pelvic pain in women. Acta Obstet Gynecol Scand. 2006;85(5):599-603.

38. Vercellini P, Barbara G, Somigliana E, et al. Comparison of contraceptive ring and patch for the treatment of symptomatic endometriosis. Fertil Steril. 2010 May 1;93(7):2150-61.

39. Zupi E, Marconi D, Sbracia M, et al. Add-back therapy in the treatment of endometriosis-associated pain. Fertil Steril. 2004 Nov;82(5):1303-8.

40. Vercellini P, De Giorgi O, Oldani S, et al. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol. 1996 Aug;175(2):396-401.

41. Parazzini F, Di Cintio E, Chatenoud L, et al. Estroprogestin vs. gonadotrophin agonists plus estroprogestin in the treatment of endometriosis-related pelvic pain: a randomized trial. Gruppo Italiano per lo Studio dell'Endometriosi. Eur J Obstet Gynecol Reprod Biol. 2000 Jan;88(1):11-4.

42. Onwude JL, Thornton JG, Morley S, et al. A randomised trial of photographic reinforcement during postoperative counselling after diagnostic laparoscopy for pelvic pain. Eur J Obstet Gynecol Reprod Biol. 2004 Jan 15;112(1):89-94.

43. Ghaly AFF. The psychological and physical benefits of pelvic ultrasonography in patients with chronic pelvic pain and negative laparoscopy. A random allocation trial. Journal of Obstetrics & Gynaecology. 1994;14:269-271.

44. Zondervan KT, Yudkin PL, Vessey MP, et al. Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database. Br J Obstet Gynaecol. 1999 Nov;106(11):1149-55.

Internet Citation

{Provided by AHRQ} Authoring EPC, Title, Comparative Effectiveness Review: Number ##. AHRQ Publication Number No. 0#-###, Month 200#. Agency for Healthcare Research and Quality, Rockville, MD. http://www.effectivehealthcare.ahrq.gov/xxxxxxx

Evidence Report

Introduction

Overview

Chronic pelvic pain is defined by the American College of Obstetrics and Gynecology as intermittent or constant pain over at least 6 months in the lower abdomen or pelvic area. Pain may occur in the lower abdomen or pelvis, including the abdominal wall at or below the umbilicus, lumbrosacral back or the buttocks. The pain is sufficiently severe that it impedes activities of daily living or causes functional disability or leads to medical care.[1-5] In practice and in current research, the diagnosis of CPP may be made as early as 3 months after onset of pain.[6]

Noncyclic chronic pelvic pain (CPP) is the focus of this review. Noncyclic CPP excludes chronic pelvic pain that is limited to dysmenorrhea (pain with menstruation), or dyspareunia (pain with intercourse), dyschezia (pain with bowel movement), or dysuria (pain with urination).[2, 3] Noncyclic CPP is sometimes described simply as "chronic pelvic pain" in the literature, since many subdivide chronic pelvic pain into dysmenorrhea, dyspareunia, and nonmenstrual CPP.[1]

For this review, we defined noncyclic CPP as pain that has persisted for more than 3 months, is localized to the anatomic pelvis (lower abdomen below the umbilicus), and is of sufficient severity that it causes the patient to become functionally disabled or to seek medical care. CPP as described throughout this review refers to noncyclic or mixed cyclic/noncyclic pelvic pain unless otherwise noted.

Prevalence

Given the lack of established definitions for CPP, prevalence estimates vary. The prevalence of CPP was estimated to range from 4 percent to 43 percent in a systematic review of worldwide prevalence including 18 studies of variable quality.[7] Across 3 studies with representative samples, the prevalence range of CPP was 2 percent to 29 percent.[7] One of these studies, conducted in Australia, estimated a point prevalence of 3.8 percent in women aged 15 to 73, a prevalence comparable with that of asthma (3.7 percent) and chronic back pain (4.1 percent).[8]

Health Impact

CPP in women is common and difficult to treat.[4, 9] The diagnosis of CPP is often delayed, leading to frustration and dissatisfaction for both the woman and her clinician. Treatments for CPP may often yield unsatisfactory results.[10]

CPP, both cyclic and noncyclic, accounts for about 1 in 10 outpatient gynecology visits and is the indication for an estimated 15 percent to 40 percent of laparoscopies and 12 percent of hysterectomies in the United States.[9, 11] In a Gallup poll of 5,325 women in the United States, 557 indicated they had CPP within the previous month. Over half of these respondents noted that CPP interfered with mood and energy to complete daily activities and 15 percent reported work absenteeism.[10]

An estimated $1.2 billion per year is spent on outpatient management of CPP in the United States (adjusted for inflation from $880 million in 1996). In addition, the total indirect cost due to time lost from work is estimated to be $760 million per year (adjusted for inflation from $555 million in 1996).[10] CPP carries a significant quality of life burden in terms of sexual functioning, depression, fatigue, and physical limitations and disability associated with pain.[10]

An individual woman's experience of CPP is inevitably affected by a combination of physical, psychological and social factors, and the condition's impact on quality of life can be substantial. Women with CPP tend to report lower general physical health scores than women without pain.[12-15] Women with CPP describe loss, social isolation, and effects on relationships and have a high incidence of comorbidity, sleep disturbance, and fatigue. A community based study found that 41 percent of women with CPP had not seen a health care provider in the previous year,[12, 13] suggesting that most women are coping outside the system.

Etiology

The causes of CPP are poorly understood, and diagnosis of an underlying cause is complicated because the pain is rarely associated with a single underlying disorder or contributing factor;[4] Howard outlined more than 60 diseases and conditions associated with CPP.[4] CPP is frequently reported in the presence of both gynecologic and nongynecologic diagnoses, including endometriosis, intraabdominal adhesions, myosfascial pain disorders, irritable bowel syndrome (IBS) and interstitial cystitis (IC)/painful bladder syndrome (PBS).[1, 5, 16-26]

Empirically established relationships among putative causes of CPP and CPP are variable. For example, adhesions are often thought to be a frequent cause of pelvic pain; in fact there is little difference in the prevalence of adhesions found in women with and without CPP.[22, 24] It is thus unknown whether associated factors and conditions are etiologic (causal) in nature, or are comorbidities with distinct etiologies from the CPP. Regardless, from the patient perspective, the presence of one or more conditions may coalesce in a common presentation of pain. For the purposes of treatment and research in this area, identifying clinical comorbidities that are in fact associated with a CPP diagnosis may affect clinical practice by guiding decisions about diagnostic and treatment processes.

Comorbidities

A number of conditions are reported along with CPP in the literature. Among these comorbidities are IBS, with studies reporting IBS prevalence of 35 to 65 percent in women with CPP.[27-29] As many as 85 percent of women with CPP meet some criteria for IC or PBS.[11, 30] Prevalence estimates for endometriosis in women with CPP range from 33 to70 percent.[31, 32] Depression and sleep disorders are also commonly reported among women with CPP.[33]

CPP is also associated with numerous general, gynecologic, and obstetric factors including abuse (childhood physical or sexual abuse, lifetime sexual abuse); psychological morbidity (anxiety, depression, sleep disorders, hysteria, somatization, drug abuse, alcohol abuse); obstetric history (previous miscarriage, cesarean birth); gynecologic history (longer menstrual flow, presence of endometriosis, clinically suspected pelvic inflammatory disease, pelvic adhesions).[7] Anxiety, depression, sexual problems, and sleep disorders are common in CPP in women.[7, 33, 34]

The relationships between CPP and sexual or physical abuse are complex. Many studies reporting such associations are cross-sectional and performed in settings of secondary and tertiary care.[35, 36] In these selected populations, some studies reported that women with chronic pain in general are more likely to report physical or sexual abuse as children than pain-free women. Those who experienced CPP were more likely to report past sexual abuse than women with another type of chronic pain;[37-41]child sexual abuse may be a correlate of continuing abuse

and concomitant development of depression, anxiety or somatization, which then predispose the individual to the development or presentation of CPP.[37, 38, 42]

Evaluation of CPP

Evaluation of CPP and definitive diagnosis of the cause are complex. Indeed, one retrospective study from the United Kingdom found that more than 25 percent of women with CPP never received a definitive diagnosis after nearly 4 years of follow-up.[8, 43] A thorough patient evaluation including pain history and pain mapping is a critical step in determining the potential etiology and an initial therapeutic course and in establishing a rapport between the clinician and patient.[44-46] The experience of pain will inevitably be affected by physical, psychological and social factors. Thus CPP may also be viewed from a biopsychosocial perspective, which considers the contributions of organic pathology, patient beliefs, coping skills, social interactions, and overlapping conditions to the experience of pain.[47]

Surgical approaches to evaluation include laparoscopy. CPP is the reported indication for at least 40 percent of diagnostic and therapeutic laparoscopic procedures in the United States.[4, 48]Endometriosis, pelvic adhesions, chronic pelvic inflammatory disease, and ovarian cysts are the diagnoses most commonly made by laparoscopy in patients with a preoperative diagnosis of CPP;[4, 7, 22] however, at diagnostic laparoscopy, a substantial proportion of women with CPP (24 to 55 percent) have no obvious pathological cause for their pain.[22, 49] Even when pathology is found, it may not be causing the CPP, and a definitive cause and diagnosis are often not determined.

Interventions

Empirical treatment, or treatment based on clinician experience and observation as the basis for decision-making, rather than systematic logic or solid evidence, for CPP as a symptom is increasingly recommended as standard initial management.[1, 50, 51] For example, current guidelines from the American College of Obstetricians and Gynecologists include an empirical trial of gonadotropin releasing hormone (GnRH) agonists for women who are suspected to have CPP and endometriosis and do not desire a definitive diagnosis or wish to defer surgical investigation.[1]

A range of therapeutic interventions are used in clinical practice. Pharmacologic therapies include narcotic and nonnarcotic analgesics; antineuropathics; serotonin reuptake inhibitors; botulinum A toxin injections; and hormonal therapies such as cyclic combined hormonal contraceptives, continuous combined hormonal contraceptives, progestogens, GnRH, and aromatase inhibitors.[1] Surgical interventions, which may be performed laparoscopically or in open surgical procedures, include hysterectomy (with or without oophorectomy or salpingo-oophorectomy), utero-sacral nerve ablation, presacral neurectomy, lysis of adhesions, and utero-sacral ligament resection. CPP (both cyclic and noncyclic) has been listed as the principal preoperative indication for 10 percent to 18 percent of hysterectomies in the United States.[9, 52-59]

Other therapeutic interventions used in clinical practice include behavioral therapies such as biofeedback, psychotherapy, cognitive behavioral therapy, and support groups. Among allied health approaches, physical therapy, dietary modification, and exercise therapy have been used to treat CPP. Complementary and alternative modalities include hypnosis, herbal medicine, massage, acupuncture, meditation, and stress-reduction approaches. A recent Cochrane review of 14 RCTs of interventions for CPP (excluding studies of patients with pain “known to be caused

by" endometriosis, primary dysmenorrhea [period pain with onset at menarche], pain due to active chronic pelvic inflammatory disease, or irritable bowel syndrome)[2] noted that the range of effective therapies for CPP is limited and that recommendations for their use are based largely on single studies. A recent narrative review[60] similarly concluded that few treatment modalities have demonstrated benefit for relieving CPP symptoms.

Summary

CPP is a common and broadly defined condition. Multiple interventions are used empirically in clinical practice to manage potential etiologies and to treat pain symptoms. The condition is frequently complicated by comorbidities, including depression, anxiety, IBS, and idiopathic pain disorders, and treatment must target symptoms across a spectrum of conditions. Existing literature cites a range of treatment options for women with CPP, many of which have not been tested in rigorous studies.

Scope and Key Questions

Scope of the Report

Evidence reviews of therapeutics seek to identify and systematically summarize objective information about the evidence related to factors including the:

- Effectiveness of specific, well-defined treatments
- Relative benefit of one treatment over another
- Common side effects and serious risks of a treatment.

We focused this review on therapies for women over the age of 18 with noncyclic or mixed cyclic/noncyclic chronic pelvic pain. Throughout this review, CPP refers to noncyclic or mixed cyclic/noncyclic pelvic pain unless otherwise noted.

Key Questions

We have synthesized evidence in the published literature to address these key questions (KQs):

KQ1: 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, IC/PBS, complex regional pain syndrome, vulvodynia, functional abdominal pain syndrome, low back pain, headache, and sexual dysfunction?
KQ2: 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?
KQ3: What is the evidence that surgical outcomes differ if the etiology of noncyclic/mixed cyclic and noncyclic CPP is identified after surgery?
KQ4: 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?
KQ5: 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)?

Organization of This Evidence Report

The Methods section describes our processes including our search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, and our method for extraction of data into evidence tables and compiling evidence. We also describe the approach to grading of the quality of the literature and to evaluating the strength of the body of evidence.

The Results sections presents the findings of the evidence report, synthesizing them by key question and outcomes reported. We report the number and type of studies identified and we differentiate between total numbers of publications and unique studies. In key question 1, we discuss the prevalence of selected comorbidities. In key questions 2 and 4, we emphasize the effect of treatment on pain and functional status, quality of life, and patient satisfaction. Key questions 3 and 5 describe evidence for differences in surgical outcomes when an etiology for CPP is identified after surgery and for defining a treatment trajectory or pathway once an intervention for CPP is not successful.

The final section of the report discusses key findings and expands on methodologic considerations relevant to each key question. We also outline the current state of the literature and challenges for future research in CPP.

The report includes a number of appendixes to provide further detail on our methods and the studies assessed. The appendixes are as follows:

- Appendix A: Search Strategy
- Appendix B: List of Excluded Studies
- Appendix C: Evidence Tables
- Appendix D: Data Extraction Forms
- Appendix E: Quality of the Literature
- Appendix F: Applicability Summary Tables.

We also include a list of abbreviations and acronyms at the end of the report.

Uses of This Report

This evidence report addresses the key questions outlined previously using methods described in the report to conduct a systematic review of published literature. We anticipate that the report will be of value to clinicians who treat women with CPP, including gynecologists and other physicians who provide gynecologic care, nurses and advanced practice nurses, psychologists and psychiatrists, physical therapists and allied health professionals.

In addition, this review will be of use to the National Institutes of Health, Centers for Medicare & Medicaid Services, and the Health Resources and Services Administration–all of which have offices or bureaus devoted to women's health issues. This report can bring practitioners up to date about the current state of evidence, and it provides an assessment of the quality of studies that aim to determine the outcomes of therapeutic options for the management of CPP. It will be of interest to women affected by CPP and their families because of the high prevalence of CPP, significant personal costs associated with it, and the recurring need for women and their health care providers to make the best possible decisions among numerous options.

Researchers can obtain a concise analysis of the current state of knowledge in this field. They will be poised to pursue further investigations that are needed to understand best approaches to therapies for women with CPP.

Methods

Topic Development and Refinement

The topic for this report was nominated in a public process. We drafted the initial key questions and analytic framework and refined them with input from key informants. After approval from the Agency for Healthcare Research and Quality (AHRQ), the questions and framework were posted to a public Web site. The public was invited to comment on these questions.

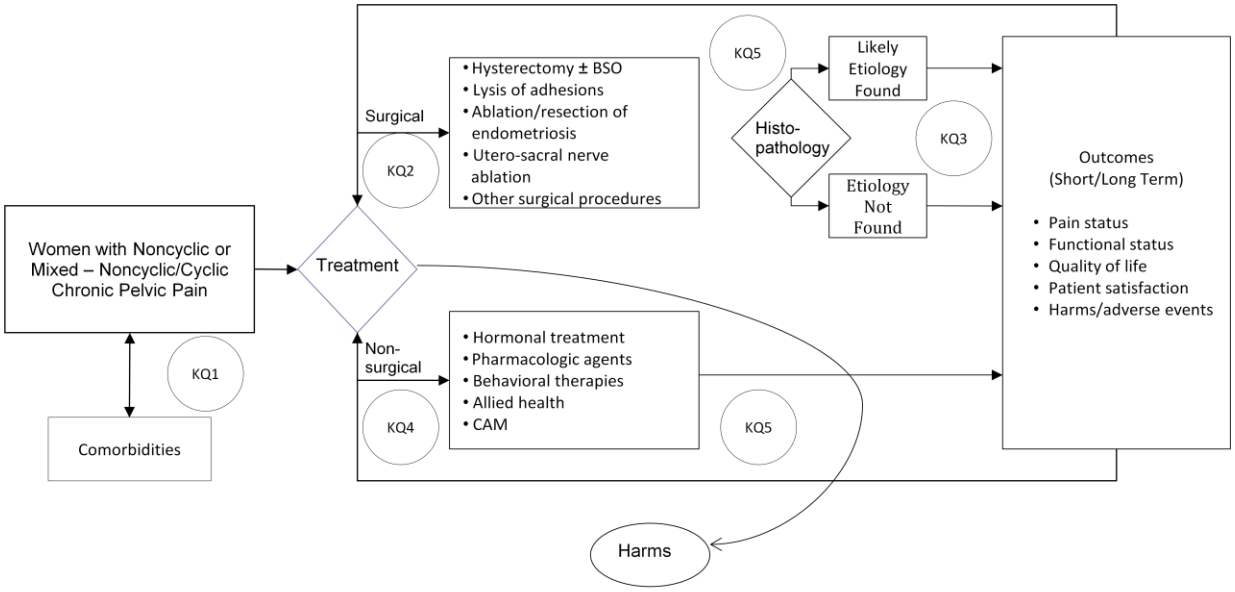
After reviewing the public commentary, we drafted final key questions (KQ) and submitted them to AHRQ for approval. We identified technical experts on the topic of chronic pelvic pain in women in the fields of gynecology and women's health to provide assistance during the project. The Technical Expert Panel (TEP) contributed to the AHRQ's broader goals of (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential customers and users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included 5 members serving as technical or clinical experts. To ensure robust, scientifically relevant work, we called on the TEP to provide reactions to work in progress. TEP members participated in conference calls and discussions through e-mail to:

- Refine the analytic framework and key questions at the beginning of the project;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria;
- Provide input on assessing the quality of the literature.

Analytic Framework

We developed the analytic framework (Figure 1) based on clinical expertise and refined it with input from our key informants and TEP members. The framework summarizes the process by which women with noncyclic chronic pelvic pain (CPP) make and modify treatment choices. Treatment choices include surgical or nonsurgical approaches and may lead to outcomes including changes in pain status (e.g., resolution of pain, continuing pain, continued need for pain medication), patient satisfaction, quality of life, or harms/adverse effects. In addition, outcomes may vary by diagnosis in those patients receiving a confirmed diagnosis for the etiology of their CPP.

Figure 1. Analytic framework for therapies for women with CPP



BSO=bilateral salpingo-oopherectomy; CAM=complementary and alternative medicine; KQ=Key Question

Literature Search Strategy

Databases. We employed search strategies provided in Appendix A to retrieve research on the treatment of CPP in women. Our primary literature search employed 4 databases: MEDLINE® via the PubMed interface, PsycINFO (psychology and psychiatry literature), EMBASE Drugs and Pharmacology, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) database. Our search strategies used a combination of subject heading terms appropriate for each database and key words relevant to CPP (e.g., chronic pelvic pain, pelvic pain). We limited searches to the English language and literature published since 1990, when laparoscopic techniques became more widely used.

We also manually searched the reference lists of included studies and of recent narrative and systematic reviews and meta-analyses addressing CPP. We also invited TEP members to provide additional citations.

Grey literature. The AHRQ Scientific Resource Center also searched for information on the following specific medications used to treat CPP. We requested grey literature information on these drugs and devices as they are either commonly used and have a number of known side effects or are beginning to be used in the CPP population and have not yet been well-reported in the published literature (e.g., aromatase inhibitors):

- Medroxyprogesterone
- Gonadotropin releasing hormone (GnRH) agonists (with or without add-back estrogen therapy including buserelin, goserelin, leuprolide, and nafarelin)

- Selective progesterone receptor modulators (SERMs) (mifepristone and ulipristal acetate);
- Selective estrogen receptor modulators (tibolone, ranitidine, clomiphene, and tamoxifen);
- Aromatase inhibitors (anastrozole and letrozole); and
- Transcutaneous electrical nerve stimulation (TENS).

The Scientific Resource Center sought grey literature in resources including the websites of the US Food and Drug Administration and Health Canada and clinical trials registries such as ClinicalTrials.gov. We also gave manufacturers of these medications and devices an opportunity to provide additional information.

Search terms. Controlled vocabulary terms served as the foundation of our search in each database, complemented by additional keyword phrases. We also employed indexing terms when possible within each of the databases to exclude undesired publication types (e.g., reviews, case reports, news), items from non-peer-reviewed journals, and items published in languages other than English.

Our searches were executed between September 2010 and January 2011. Appendix A provides our search terms and the yield from each database. We imported all citations into an electronic database created using EndNote.

Process for Study Selection

We developed criteria for inclusion and exclusion based on the patient populations, interventions, outcome measures, and types of evidence specified in the key questions and in consultation with the TEP. Table 1 summarizes criteria.

Table 1. Inclusion and exclusion criteria

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–present
Publication languages	English only

Table 1. Inclusion and exclusion criteria (continued)

Category	Criteria

Admissible evidence (study design and other criteria)	Admissible designs
	• Controlled trials, prospective cohort studies with N ≥ 50, cross-sectional studies
	• Case series with N ≥ 100 and harms or prevalence data relevant to the KQs
	
	Other criteria
	• 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 will 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 for CPP:
	  ○ Treatment modality aimed at modifying CPP symptoms
	  ○ Short- and long-term outcomes (including 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

CPP=noncyclic chronic pelvic pain; KQ=key question; N=number; PICOTS=population, intervention, comparison, outcomes, timing, setting

For this review, the relevant population for all KQ was adult women (≥ age 18) with noncyclic or mixed cyclic/noncyclic CPP, which we defined as pain that has persisted for more than 3 months, is localized to the anatomic pelvis (lower abdomen below the umbilicus), and is of sufficient severity that it causes the patient to become functionally disabled or to seek medical care. CPP as described throughout this review refers to noncyclic or mixed cyclic/noncyclic pelvic pain unless otherwise noted.

Studies needed to provide adequate information to ensure that participants fell within the target age range and pain criteria. For studies with populations including women under age 18, we retained the study if we could infer that at least 80 percent of the study participants were over the age of 18. Similarly, some studies included women with cyclic chronic pelvic pain and women with noncyclic chronic pelvic pain. We retained studies with participants with both cyclic and noncyclic/mixed chronic pelvic pain if at least 80 percent of the population was composed of women with noncyclic/mixed chronic pelvic pain.

We also applied this criterion to studies including both women and men, retaining studies that included men if the study population was composed of at least 80 percent women with CPP. We attempted to extract data only on the population of interest (adult women with noncyclic/mixed CPP) where possible. We chose the figure of 80 percent as we considered studies in which a majority of participants were within our target age range (18 and older), or had noncyclic CPP, or included a low proportion of men as providing data applicable to the population of adult women with noncyclic CPP.

The inclusion in the study population of fewer than 20 percent of participants with characteristics outside our inclusion criteria of the review may introduce bias in the results, but not to such a degree that the results would not be useful. As appropriate, we note in our discussion of studies that results apply to a heterogeneous age range or pain group or include data from some male participants.

We excluded studies that included fewer than 50 total participants for studies addressing KQ 2-5 or fewer than 100 total participants for studies addressing KQ1 or providing data about nonsurgical harms. We selected these criteria as a minimum threshold for comparing interventions and based on our assessment of factors including prevalence, loss to followup, clinical effect size, and statistical power.

We accepted study designs including controlled trials and prospective cohort studies addressing the effectiveness of surgical or nonsurgical approaches (KQ2, KQ4), outcomes if an etiology for CPP is identified (KQ3), or effectiveness of one intervention over another to treat persistent CPP (KQ5). We accepted prospective or retrospective case series or cross- sectional studies with at least 100 participants with CPP and addressing the prevalence of comorbidities of interest (KQ1) or harms of nonsurgical therapies (KQ4).

We selected the comorbidities of interest based upon reporting in the CPP literature. We extracted data regarding a study's use of validated tools to diagnose comorbidities or the provision of an operational definition for a comorbid condition. As described below, we factored the use of a validated tool into our quality assessment of studies providing data on the selected comorbidities.

To gauge the relevance of research published in other languages, we located non-English literature for the time period of interest using our MEDLINE search strategy and identified 168 citations. Twenty-nine of these citations appeared potentially relevant on a title scan. We reviewed the abstracts of 28 of these, and none met our review criteria. We believed that the one study for which we could not locate an abstract would not substantially alter the findings of the review and excluded non-English studies.

In addition, we excluded studies that:

- addressed pelvic pain related to cancer or pregnancy as the etiology of and treatment for these entities is significantly different from CPP related to other or unknown causes;
- did not report information pertinent to the key questions;
- were published prior to the year 1990 and the widespread use of laparoscopic techniques and introduction of medications such as serotonin reuptake inhibitors used to treat CPP; and
- were not original research.

Once we identified articles through the electronic database searches, review articles, and bibliographies, we examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated each abstract for inclusion or exclusion, using an Abstract Review Form (Appendix D). If one reviewer concluded that the article could be eligible for the review based on the abstract, we retained it for full text assessment. The group included expert clinicians (JA, SR, AY, FL) and health services researchers (RJ, NS). Two reviewers assessed the full text of each included article using a standardized form (Appendix D); disagreements between reviewers were resolved by a third-party adjudicator.

Data Extraction and Data Management

The staff members and clinical experts who conducted this review jointly developed the evidence tables, which were used to extract data from the studies. We designed the tables to provide sufficient information to enable readers to understand the studies, including issues of study design, descriptions of the study populations (for applicability), description of the intervention, and baseline and outcome data on constructs of interest. Our outcomes of interest included:

- Pain status (reduction in pain, pain recurrence, subsequent intervention for unresolved or worsening pain);
- Functional status (activities of daily living, sexual functioning);
- Quality of life;
- Patient satisfaction with pain management; and
- Harms or adverse effects of nonsurgical interventions.

The team abstracted several articles into evidence tables and then discussed the utility of the table design as a group. We repeated this process through several iterations until we decided that the tables included the appropriate categories for gathering the information contained in the articles. All team members shared the task of initially entering information into the evidence tables. Another member of the team also reviewed the articles and edited all initial table entries for accuracy, completeness, and consistency. The full research team met regularly during the article extraction period and discussed global issues related to the data extraction process.

Where available, we also captured data on potential risk factors related to CPP or conditions thought to occur commonly with CPP. These data included:

- History of sexual or physical abuse;
- History of pelvic surgery;
- Pregnancy-related risk factors (e.g., history of Caesarean births, vaginal births, operative vaginal birth, genital tract trauma, pregnancy termination); and
- History of comorbidities of interest (anxiety, depression, dysmenorrhea, fibromyalgia, headache, irritable bowel syndrome (IBS), interstitial cystitis/painful bladder syndrome (IC/PBS), low back pain, and sexual dysfunction).

This list of comorbidities represents conditions thought to occur frequently with CPP and was determined in consultation with our TEP.

The final evidence tables are presented in their entirety in Appendix C. Studies are presented in the evidence tables alphabetically by the last name of the first author within each year. When possible to identify, analyses resulting from the same study were grouped into a single evidence table.

Individual Study Quality Assessment

We used a components approach to assessing the quality of individual studies, following methods outlined in the EPC's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[61] Decision rules regarding application of the tools were developed *a priori* by the research team. We developed separate quality assessment approaches for randomized controlled trials (RCTs), observational studies, and studies addressing the prevalence of comorbidities. Two reviewers independently assessed each study, with disagreements between assessors resolved via a third adjudicator.

We assessed each domain described below individually and integrated them for an overall quality level as described in the Determining Quality Levels section. We assessed studies as having "met" or "not met" a criterion; where relevant, criteria could also be judged as not applicable (NA) to a study. For the final integration of the assessment of quality, 3 levels were possible: good, fair, and poor.

We describe the individual quality components below and report individual quality assessments for each study in Appendix E.

Randomized Controlled Trials

We assessed quality factors recommended in the Evidence Based Practice Centers' (EPCs) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* and in the *Cochrane Handbook*.

Sequence generation. We assessed study randomization by considering the following questions:

1. Was the assignment randomized?
2. Was the method used to generate the sequence of randomization described and was it appropriate?

We considered the following elements in determining the appropriateness of a study's randomization methods: Were random techniques like computer-generated, sequentially numbered opaque envelope used? Were technically non-random techniques, like alternate days of the week used?

Scoring. Studies providing a description of a truly random allocation technique were assessed as "met" for this element.

Allocation concealment. We considered 4 elements to assess allocation concealment:

1. Was the allocation to study groups (and interventions) adequately concealed from patients/ participants?
2. Was the allocation to study groups (and interventions) adequately concealed from investigators?
3. Was the allocation to study groups (and interventions) adequately concealed from clinical providers/caregivers?
4. Was the allocation to study groups (and interventions) adequately concealed from outcome assessors?

Scoring. We defined adequate concealment as reasonable attempts (e.g., non-investigators involved in allocation, appropriate sham treatments used, etc.) by investigators to conceal allocation groups. We assessed these criteria as met if the study provided such evidence of allocation concealment.

Incomplete outcome data addressed. We considered 4 elements to assess the completeness of outcomes data reporting:

1. Was complete information about participant flow provided, such as CONSORT diagram or equivalent information (numbers at random assignment; numbers receiving intended intervention; numbers completing protocol; and numbers analyzed for primary outcome, drop-out, lost to follow-up)?
2. Was an intention-to-treat analysis (as assigned conducted and reported) performed appropriately?

3. Were incomplete/missing outcome data adequately reported?
4. Were missing outcome data managed by an accepted method?

Scoring. We considered acceptable methods of missing data management as either last observation carried forward; mean/median imputation; worst outcome imputation; or longitudinal regression imputation.

Selective outcome reporting. We assessed this domain using a single question: Was the primary outcome planned and described in the Methods section?

Scoring. Studies describing an *a priori* primary outcome determination were assessed as meeting this criterion.

Other bias. We assessed whether the study was largely free of other bias by considering the following elements: Was the trial stopped early for benefit? Was there an extreme baseline imbalance? Was there a substantive conflict of interest which posed a substantive, important threat to validity of the results?

Scoring: We scored studies as meeting this criterion if there was no evidence of such biases.

Sample size and power. We assessed this domain be determining whether an *a priori* sample size calculation was provided for the primary outcome.

Scoring. We scored studies as meeting this criterion if evidence of a sample size calculation was provided.

Statistical analysis. We considered the suitability of a study's analysis using the following questions:

1. Was statistical analysis appropriate for the study design performed?
2. Were the statistical results reliable?

Scoring. We scored studies as having "met" these criteria if our judgment was that the statistical analysis and results were appropriate and reliable for the stated study design and outcome. A glaring inconsistency or statistical error would result in a score of 'not met'.

Drop-out proportion. We evaluated studies for this domain using the question: What proportion of enrolled participants assigned to an intervention declined to continue the assigned intervention?

Scoring. We considered studies with a drop-out rate of less than or equal to 10 percent as having "met" this criteria. We assessed studies with a greater than 10 percent or unreported rate as having "not met" the criterion.

Follow-up. We assessed the adequacy of follow-up by determining what proportion of enrolled population was present or accessible at the time of the primary followup.

Scoring. We considered studies with a rate of less than or equal to 20 percent loss as having "met" this criterion. Studies with greater than 20 percent loss or not reporting the percentage were scored as having "not met" this criterion.

Observational Studies

For observational studies we considered these domains: (1) the selection of the study groups; (2) the comparability of the study groups; and (3) the ascertainment and measurement of either

the exposure/intervention or outcome of interest for case-control or cohort studies respectively; (4) allocation concealment; and (5) methods for limiting bias and confounding.

For example, for a cohort study, the fundamental criteria included: representativeness of cohort, selection of nonexposed cohort, ascertainment of exposure, outcome of interest, comparability of cohorts, assessment of outcome, adequate duration of follow-up, and adequate follow-up of cohort. Other sources of bias would include baseline imbalances, source of funding, early stopping for benefit, and appropriateness of crossover design.

Selection of participants in study groups. We considered 3 elements to evaluate a study's risk of bias in the selection of study group participants:

1. Were the characteristics of the participants/patients included in the study groups clearly described?
2. Were the inclusion and/or exclusion criteria described?
3. Were the criteria applied equally to all groups?

Scoring. We scored studies as having "met" this criterion if related data were provided.

Comparability of the study groups. We used the following questions to assess this domain:

1. Was there an assessment of baseline comparability, with regard to confounders (disease status, risk factors, prognostic factors, case-mix adjustment) for the most important factors (attempts to balance the groups by design), and did this demonstrate comparability?
2. Were concurrent controls used?

Scoring. We scored studies as having met these criteria if related data were provided.

Intervention description. We used the following questions to assess this domain:

1. Was there a clear definition of the intervention?
2. Was the measurement method of the intervention standard, valid, and reliable?

We considered the following elements in making a determination about these questions: Did all participants receive the same intervention? Were the interventions performed by the same person? Was the intervention measured equally in all study groups?

Scoring. Studies could be assessed as having "met" or "not met" these criteria. For question 2, we scored studies of pharmacologic interventions as NA.

Outcomes. We evaluated a study's measurement of outcomes using the questions:

1. Was the method of outcome assessment standard, valid, and reliable?
2. Was the follow-up duration long enough (≥12 weeks) for the outcomes to occur?

We considered whether references for measurement instruments were provided and whether authors indicated testing of an instrument in making determinations about these questions.

Scoring. Studies could be assessed as having "met" or "not met" these criteria.

Allocation concealment. We used the following questions to assess allocation concealment:

1. Were the outcome assessors blind to the intervention/outcome status?
2. If assessors were blinded, was concealment adequate?

Scoring. Studies could be assessed as having "met" or "not met" these criteria.

Outcome data reporting. We judged the quality of studies' outcome reporting using the 2 questions below.

1. Were incomplete/missing outcome data adequately reported?
2. Were the data managed by an accepted method?

We considered acceptable data management methods as last observation carried forward; mean/median imputation; worst outcome imputation; or longitudinal regression imputation.

Scoring. Studies could be assessed as having "met" or "not met" these criteria..

Selective outcome reporting. To assess this factor, we considered whether a primary outcome was planned and described in a study's methods.

Scoring. Studies could be assessed as having "met" or "not met" these criteria..

Other bias. We evaluated a study's handling of potential biases using the questions:

1. Were methods appropriate for dealing with any design-specific issues such as recall bias, interviewer bias, etc.?
2. Was there a substantive conflict of interest which posed an important threat to validity of the results?

We considered factors such as unclear reporting of findings in industry-sponsored trials and reporting interim versus final data (e.g., reporting only 6 week data in a completed 12 week study) as examples of substantive reasons for other bias.

Scoring. Studies could be assessed as having "met" or "not met" these criteria..

Sample size and power. We considered whether an *a priori* power calculation was provided for the primary outcome in assessing this element.

Scoring. We assessed studies as having "met" or "not met" these criteria.

Statistical analysis. We used the following questions to assess a study's statistical approach and scored studies as having "met" these criteria if our judgment was that the statistical analysis and results were appropriate and reliable for the stated study design and outcome. A glaring inconsistency or statistical error would result in a score of "not met."

1. Was a statistical analysis performed that was appropriate for the study design?
2. Were the statistical results reliable?

Scoring. We assessed studies as having "met" or "not met" these criteria.

Drop-out proportion. We evaluated studies in this domain using the question: What proportion of enrolled participants assigned to an intervention (medication, cognitive behavioral therapy, etc.) declined to continue the assigned intervention? We considered the following factors in making this determination: Does the paper describe a comparison between drop-outs and the whole group? Were the reasons for drop-out or withdrawal reported? Were incomplete outcome data adequately addressed?

Scoring. We considered studies with a drop-out rate of less than or equal to 10 percent as having "met" this criteria. We assessed studies with a greater than 10 percent or unreported rate as having "not met" the criterion.

Follow-up. We assessed the adequacy of follow-up with the question, what proportion of enrolled population was present or accessible at the time of the primary followup and evaluated

the following factors in making a determination: Was loss to followup uneven across exposure groups; Did the study fail to report the number of participants available at follow-up; Were incomplete outcome data adequately addressed?

Scoring. We considered studies with no more than a 20 percent loss as having "met" this criterion. Studies with greater than 20 percent loss or not reporting the percentage were scored as having not "met" this criterion.

Confounding and effect modifiers. We evaluated observational studies for this domain using the following 4 questions:

1. For observational studies, was the approach to identifying confounding factors described?
2. Was there adequate adjustment for the potential confounding factors?
3. For observational studies, was the approach to identifying effect modifiers described?
4. Was there adequate reporting of potential effect modifiers?

We defined potentially confounding variables as having an effect on the outcome and associated with the intervention/exposure, but not on the causal pathway under study. A confounder may therefore bias the estimation of the effect of intervention/exposure on outcome if unmeasured. We considered effect modifiers to be factors that modify the effect of the putative causal factor(s) under study, by having an effect on the outcome by altering the relationship between an independent variable and a dependent variable (outcome). The effect modifier neither explains nor obscures the relationship between the causal factor of interest and the outcome – instead it alters the relationship so that under differing conditions of the effect modifier, the relationship between intervention and outcome changes in magnitude or direction.

We also considered the following elements in assessing these variables: Was the candidate variable selection discussed/noted? Was the model-building approach described? How were continuous variables handled in models? Was there restriction in design or techniques (e.g., modeling; stratified, regression, or sensitivity analyses) to correct, control, or adjust for confounding factors?

Scoring. We assessed studies as having utilized appropriate (+) or inappropriate (-) approaches.

Studies Addressing the Prevalence of Comorbidities of Interest

We assessed factors including a study's sampling method description and adequacy, sample size, response rate, specification of inclusion criteria, reporting of the age of the study population, and use of validated diagnostic criteria or operational definition of diagnosis. We assessed studies for each of the following criteria and assigned a plus if the criterion was met and a minus if not:

- **Sampling method:** The best sampling technique is random sampling, whereby a group of people are selected at random for study from a larger group (population). Each person is chosen entirely by chance, thereby reducing the likelihood of a selection bias favoring one group of people over another. Studies meeting our inclusion criteria for this question were largely intervention studies that also reported the prevalence of one or more comorbidities. If the sampling method was described, we assessed this criterion as met.
- **Sample size:** The larger the sample, the narrower will be the confidence interval around the prevalence estimate, making the results more precise. We required that studies include at least 100 participants to be assessed as having met this criterion.

- **Response rate.** Selection bias can occur if only a proportion of invited individuals participate in a survey. We set a minimum response rate of 70 percent in order for a study to be rated as having met this criterion.
- **Inclusion and exclusion criteria.** Specifying inclusion criteria allows for comparability between different prevalence data reports. Criteria should comprise information about the age range and, if appropriate, gender and ethnic group of the targeted individuals. If the inclusion and exclusion criteria were specified, then we assessed this criterion as met.

We used the above 4 criteria to establish a baseline score of zero to 4. We further considered whether a study used validated diagnostic criteria to assess comorbidities of interest or provided an operational definition for a given comorbidity:

- **Validated diagnostic criteria or operational definition.** We sought studies that addressed the prevalence of comorbidities report using validated diagnostic criteria (i.e., reference provided or discussion of testing of instrument provided), if such criteria existed when the study was conducted. If no validated criteria exist for a given comorbidity (e.g., vulvodynia, dysmenorrhea, fibromyalgia, IC/PBS, complex regional pain syndrome, functional abdominal pain syndrome, low back pain, and headache) or a validated tool was not used, we required that studies report an operational definition to meet this criterion. We considered operational definitions broadly as statements explaining how the investigators defined the comorbidity (e.g., an explanation of dysmenorrhea as painful menstrual periods). We scored each comorbidity reported in a study separately, assigning 2 points if the comorbidity was diagnosed with validated criteria or 1 point if the study provided an operational definition for the criteria, and zero points if no explanation of the criteria for the comorbid diagnosis was provided.

Determining Quality Levels

For RCTs, we considered a "good" study as one that met all criteria. We considered studies that were assessed as not meeting a factor in 3 or more domains (e.g., sequence generation, allocation concealment, sample size and power, etc.) as poor quality. Studies not meeting criteria in one or 2 domains were considered fair quality.

For observational studies, we considered those meeting all criteria as good quality studies; those assessed as not meeting criteria in one to 4 domains as fair quality; and those not meeting criteria in 5 or more domains as poor quality.

For studies addressing the prevalence of comorbidities the minimum possible score was zero, and the maximum possible score was 6. In practice, the lowest score was 3 and the highest score was 6. We considered studies achieving 6 total points as good quality; those receiving 5 points as fair quality; and those receiving 4 or fewer points as poor quality. Table 2 provides more information about study quality levels.

Table 2. Description of study quality levels

Quality level	Description
Good	Good studies are considered to have the least bias and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias; measure outcomes; analyze and report results.

Table 2. Description of study quality levels (continued)

Quality level	Description
Fair	Fair studies are susceptible to some bias, but probably not sufficient to invalidate the results. A study may be missing information, making it difficult to assess limitations and potential problems. As the "fair-quality" category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	Poor studies are subject to significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Data Synthesis

There was significant heterogeneity among studies reporting therapeutic results for women with CPP, including heterogeneity of population inclusion criteria, heterogeneity of intervention, and heterogeneity of outcome measures. Therefore, it was not appropriate to perform any meta-analysis.

Grading the Body of Evidence for Each Key Question

We evaluated the overall strength of the evidence for the primary outcomes. We used the approach to strength of evidence as described in the EPCs' *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[61] We assessed the strength of evidence for key outcomes identified by the clinical investigators to be most clinically important: pain status (reduction in pain, recurrence of pain), subsequent intervention for the unresolved or worsening pain; and functional status (resolution/improvement of functioning). Secondary outcomes included: patient satisfaction with pain management; quality of life; and harms or adverse events.

We examined the following 4 major domains: risk of bias (low, medium, high), consistency (inconsistency not present, inconsistency present, unknown or not applicable), directness (direct, indirect), and precision (precise, imprecise). We assigned each key outcome for each comparison of interest an overall evidence grade based on the ratings for the individual domains. The overall strength of evidence could be graded as "high" (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); "moderate" (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); "low" (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect). When no studies were available for an outcome or comparison of interest, we assessed the evidence as insufficient. Two reviewers independently graded the body of evidence; disagreements were resolved through discussion or a third reviewer adjudication.

Results

This chapter presents the results of our systematic review of therapies for women with noncyclic chronic pelvic pain (CPP). We present findings for each key question (KQ) beginning with an overview of the content of the literature as a whole, including the range of study designs used, approaches assessed and participants included. The detailed analysis of the literature provides further discussion and analysis, focusing primarily on those studies that received either a good or fair quality rating.

Studies also are described in more detailed summary tables in the relevant section of text. For information on studies not included in the summary tables, please see the evidence tables in Appendix C; for information on quality scores for each study, see Appendix E.

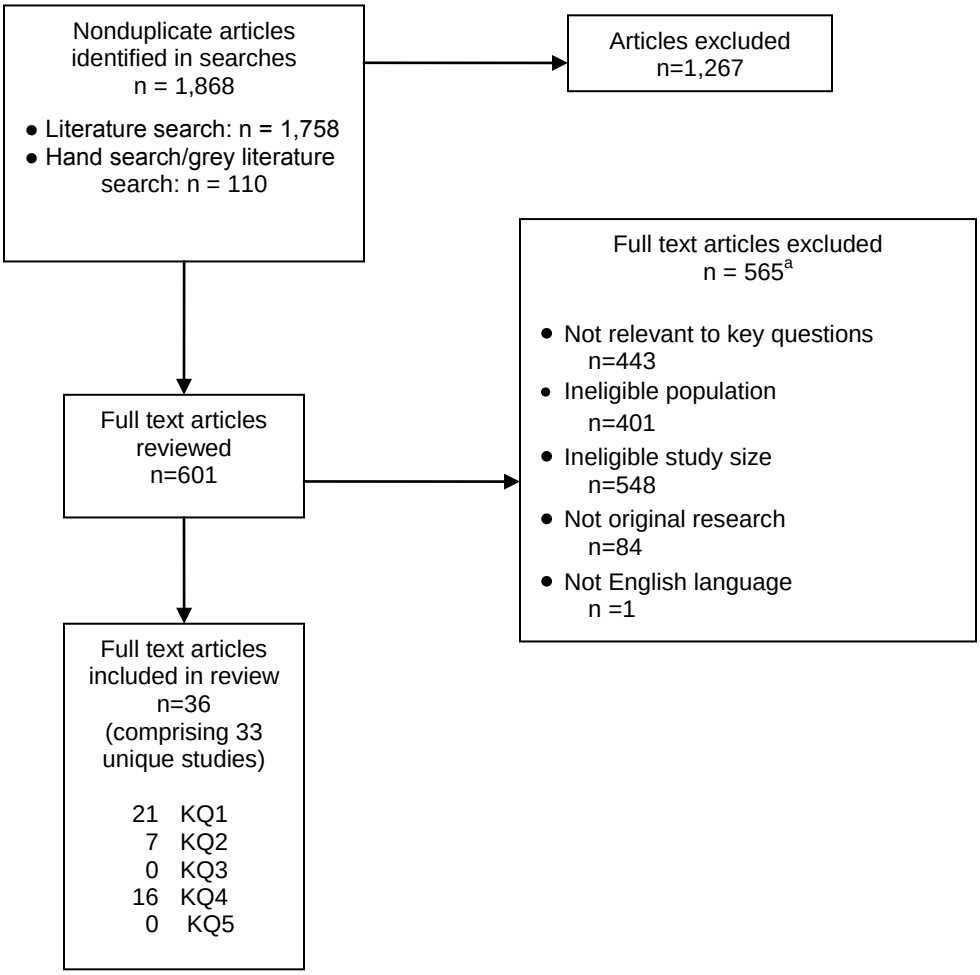
Overall, there was significant heterogeneity between studies, making it difficult to compare them; this heterogeneity was found in:

- Definitions of CPP and comorbidities of interest
- Outcome measures
- Comparators
- Duration of treatment
- Timing and length of follow-up
- Study populations.

Article Selection

Of the entire group of 1,868 citations, 601 required full text review (Figure 1). Of the 601 full text articles reviewed, we retained 36 articles (comprising 33 unique studies) and excluded 565 articles. Reasons for article exclusion are listed in Appendix B.

Figure 1. Disposition of articles located for the review



[a]The total number of articles in the exclusion categories exceeds the number of articles excluded because most of the articles fit into multiple exclusion categories; KQ=key question

The 33 unique studies described in this review included 17 randomized controlled trials (RCTs). Table 3 provides an overview of the characteristics of the literature addressing the prevalence of comorbid conditions of interest (KQ1). We considered studies that provided data exclusively for KQ1 (and did not provide data for the other key questions) to be providing cross-sectional prevalence data, regardless of the design of the study.

Table 3. Overview of noncyclic CPP literature addressing the prevalence of comorbidities of interest

Characteristic	RCTs	Prospective cohort studies	Cross-sectional studies	Total Literature
	(n=7)	(n=1)	(n=13)	(n=21)
Comorbidities reported[a]				
Back pain	2	1	3	6
Depression	0	1	2	3
Dysmenorrhea	3	0	5	8
Dyspareunia/Sexual dysfunction	4	1	10	15
Headache	2	0	0	2
Interstitial cystitis	0	0	2	2
Irritable bowel syndrome	1	1	6	8
Vulvodynia	0	1	1	2
Study population				
United States	2	1	5	8
Europe	4	0	4	8
Other	1	0	4	5
Total N participants with noncyclic CPP at intake	620	370	4,795	5,785

[a]Studies could report multiple comorbidities. CPP=noncyclic chronic pelvic pain; N=number; RCT=randomized controlled trial.

Table 4 provides an overview of studies addressing key questions focused on outcomes of surgical and nonsurgical treatment approaches (KQ2, KQ4) and those addressing the trajectory of care for women with CPP (KQ5).

Table 4. Overview of noncyclic CPP literature addressing treatment approaches

Characteristic	RCTs	nRCTs	Prospective cohort studies	Total Literature
	(n=17)	(n=1)	(n=2)	(n=20)
Intervention				
Antineuropathics	1	0	0	1
Hormonal therapies	7	1	0	8
Neuromuscular blocking agents	1	0	0	1
Adhesiolysis	1	0	0	1
LUNA	3	0	0	3
Other/combination approaches	4	0	2	6

Table 4. Overview of noncyclic CPP literature addressing treatment approaches (continued)

Characteristic	RCTs	nRCTs	Prospective cohort studies	Total Literature
Study population				
United States	2	0	2	4
Europe	13	1	0	14
Other	2	0	0	2
Last post-treatment outcome assessment				
<1 month	1	0	0	1
>1 to ≤3 months	1	0	0	1
>3 to ≤6 months	2	0	0	2
>6 to ≤12 months	8	1	2	11
>12 months	5	0	0	5
Total N participants with noncyclic CPP at intake	1,986	112	488	2,586

CPP=noncyclic chronic pelvic pain; LUNA=laparoscopic utero-sacral nerve ablation; N=number; nRCT=nonrandomized controlled trial;

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 (IBS), interstitial cystitis (IC)/painful bladder syndrome (PBS), complex regional pain syndrome, vulvodynia, functional abdominal pain syndrome, low back pain, headache, and sexual dysfunction?

Overview of the Literature

This section presents results of 24 studies, representing 21 unique study populations, meeting our review criteria and addressing co-morbidities for CPP. Here we review co-prevalence rates for conditions associated with CPP including anxiety, back pain, depression, dysmenorrhea, dyspareunia, fibromyalgia, headache, IC/PBS, IBS, sexual dysfunction, and vulvodynia. We did not locate any articles addressing temporomandibular joint pain disorder, fibromyalgia, complex regional pain syndrome, functional abdominal pain syndrome, or anxiety disorder.

Quality assessments in this section refer to the prevalence quality for the particular co-morbidity being discussed. Therefore, an individual study may have different a level of quality for each comorbidity reported. Data regarding the comorbidities most frequently reported in the literature meeting our criteria are reported in tables 5 through 7.

Key Points

- Prevalence evidence quality for most of the studies was fair or poor.
- The majority (15/24) of studies reviewed here are observational; 9 are RCTs.
- Dyspareunia (11 studies), dysmenorrhea (9 studies), and irritable bowel syndrome (8 studies) were the most frequently reported comorbidities.
- Dyspareunia prevalence in women with CPP ranged from 15 to 88 percent.
- Dysmenorrhea prevalence in women with CPP ranged from 13 to 100 percent.
- IBS prevalence in women with CPP ranged from 24-39 percent when Rome criteria were used for diagnosis.
- Understanding comorbidity prevalence in the context of a symptom-based condition like CPP is difficult; at times the same condition may be considered part of the differential diagnosis or considered to be a concomitant condition.

Detailed Analysis

Back pain. Seven studies (Table 5) reported the prevalence of back pain with rates of 1 percent to 88 percent (median 13 percent).[13, 15, 62-66] Varied terminology was used, including backache, back pain, back problems, low back pain, and muscular back pain. Only one study provided an operational definition, which was magnetic resonance imaging (MRI)-verified pathology.[63] This study was of fair quality. All 6 of the remaining studies were of poor quality. Three relied on patient report,[13, 15, 65] 2 on a physician diagnosis,[62, 64] and one did not report how the diagnosis was made.[66] It is possible that some of the participants in 2 of these studies[62, 64] are the same because they are from the same clinic during the same time period; however, it is impossible to determine the extent of overlap.

Table 5. Prevalence of back pain in women with noncyclic chronic pelvic pain

Author, Year Country Quality	N	Study Design	Terminology	Method of Diagnosis	Prevalence
Sator-Katzenschlager, 2005[63] Austria Quality: Fair	56	Cross-sectional	Low back pain	MRI-verified pathology	30%
Lamvu et al., 2006[62a] US Quality: Poor	370	Prospective cohort	Muscular back pain in methods section and low back pain in results	Physician diagnosis: definite or probable	1%
Grace et al., 2004[14, 15] New Zealand Quality: Poor	149	Cross-sectional	Back problems	Patient report of diagnosis by a medical practitioner	13%

Table 5. Prevalence of back pain in women with noncyclic chronic pelvic pain (continued)

Author, Year Country Quality	N	Study Design	Terminology	Method of Diagnosis	Prevalence
Williams et al., 2004[64, 67a] US Quality: Poor	987	Cross-sectional	Muscular back pain	Physician diagnosis: definite or probable	3%
Chung et al., 2003[65] Korea Quality: Poor	106	Cross-sectional	Low back pain	Patient report of symptoms	58%
Zondervan et al., 2001[13] UK Quality: Poor	237	Cross-sectional	Back pain or problems	Patient report of diagnosis by general practitioner/specialist	6%
Peters et al., 1991[66] Netherlands Quality: Poor	106	RCT	Backache	NR	88%

[a]These studies may have overlapping populations because they are from the same clinic during the same time period; however, it is impossible to determine the extent of overlap. MRI=magnetic resonance imaging; N=number; NR=not reported; RCT=randomized controlled trial

Depression. Three studies reported the prevalence of depression.[62, 64, 67, 68]Prevalence rates of depression ranged from 16 percent to 64 percent.[62, 64, 68] Two studies[62, 64] of good quality used the Beck Depression Inventory (BDI) to assess for depression. In a prospective cohort study of 370 women referred to a CPP specialty clinic who had CPP, 22 percent had moderate or severe depression defined as a BDI score of 19 or greater[62]. In a cross-sectional study of 987 women with CPP who were new patients at a pelvic pain clinic, 64 percent had a BDI score of 10 or higher.[64] The rationale for selecting the cut point of 10 is not identified. It is possible that some of the women in these 2 studies[62, 64] are the same because they are from the same clinic during the same time period; however, it is impossible to determine the extent of overlap.

The third study, which was of poor quality, was a placebo-controlled RCT of raloxifene for CPP in 93 women with endometriosis, in which 41 percent of women had a history of "depression" and 16 percent had a history of "depression on hormones."[68] Definitions of depression and hormones are not provided, and no information is given about how this history was obtained.

Dysmenorrhea. Nine studies (Table 6) reported the prevalence of dysmenorrhea with rates of 13 percent to 100 percent (unadjusted mean 77 percent, median 84 percent).[13, 15, 65, 69-73] One of these studies[13] was of fair quality. This cross-sectional postal survey reported an operational definition of dysmenorrhea and methods for calculating prevalence among women with CPP who had menstrual periods. The prevalence rate was 81 percent. The other 7 studies were of poor quality.

Table 6. Prevalence of dysmenorrhea in women with noncyclic chronic pelvic pain

Author, Year Country Quality	N	Study Design	Diagnostic Criteria or Operational Definition	Method of Diagnosis	Prevalence
Zondervan et al., 2001[13] UK Quality: Fair	451	Cross-sectional	Pelvic pain during or shortly before or after menstrual periods; prevalence calculated by dividing the number of women who reported dysmenorrhea during the previous 3 months by the number of women who had menstrual periods	Self-reported on postal survey	81%
Montenegro et al., 2009[69] Brazil Quality: Poor	108	Cross-sectional	Pain occurring in association with menstruation	Self-reported on history form	62%
Pitts et al., 2008[70] Australia Quality: Poor	427	Cross-sectional	Pelvic pain with periods, including irregular bleeding while on the pill or HRT	Self-reported during computer-assisted telephone interview	84%
Grace et al., 2004[15] New Zealand Quality: Poor	214	Cross-sectional	Pelvic pain with periods, including irregular bleeding while on the pill or HRT	Self-reported on postal survey	79%
Johnson et al., 2004[71] New Zealand Quality: Poor	123	RCT	NR	NR	88%
Chung et al., 2003[65] Korea Quality: Poor	106	Cross-sectional	NR	Self-reported	13%
Ling et al., 1999[72] US Quality: Poor	100	RCT	NR	Physician evaluated	100%

Table 6. Prevalence of dysmenorrhea in women with noncyclic chronic pelvic pain (continued)

Author, Year Country Quality	N	Study Design	Diagnostic Criteria or Operational Definition	Method of Diagnosis	Prevalence
Gestrinone Italian Study Group, 1996[74] Italy Quality: Poor	55	RCT	Menstrual pain, severity classified according to limitation of ability to work	Self-reported on questionnaire	100%
Vercellini et al., 1993[73] Italy Quality: Poor	57	RCT	NR	Self-reported on patient questionnaire	88%

HRT=hormone replacement therapy; N=number; NR=not reported; RCT=randomized controlled trial

Dyspareunia. Eleven studies (Table 7) reported the prevalence of dyspareunia.[10, 13, 15, 64-66, 69-72, 75] Two of the studies were of fair quality and 9 were poor. One fair quality study was a US telephone survey that included 773 women with CPP.[10] Of the 432 of those 773 women who were sexually active, 88 percent reported pain during or after sexual intercourse some, most, or all of the time in the past month. The other fair quality study was a postal survey that reported an operational definition of dyspareunia and how prevalence was calculated among women with CPP who were sexually active. The prevalence rate was 41 percent.

One poor quality study[64] reported prevalence for 3 types of dyspareunia (organic, functional, and mixed) without defining the types and/or clarifying if the rates were overlapping. Excluding this study, the prevalence rates for dyspareunia among women with CPP across all studies ranged from 15 percent to 88 percent (unadjusted mean 54 percent, median 55 percent). See also sexual dysfunction below.

Table 7. Prevalence of dyspareunia in women with noncyclic chronic pelvic pain

Author, Year Country Quality	N	Study Design	Terminology and Definition	Method of Diagnosis	Prevalence
Zondervan et al., 2001[13] UK Quality: Fair	432	Cross-sectional	Dyspareunia: Pain that occurs with intercourse Prevalence calculated by dividing the number of women who reported dyspareunia during the previous 3 months by the number of women who were sexually active	Self-reported on postal survey	41%
Mathias et al., 1996[10] US Quality: Fair	432	Cross-sectional	Dyspareunia: pain during or after sexual intercourse some, most, or all of the time in the past month	Self-reported during telephone survey	88%

Table 7. Prevalence of dyspareunia in women with noncyclic chronic pelvic pain (continued)

Author, Year Country Quality	N	Study Design	Terminology and Definition	Method of Diagnosis	Prevalence
Montenegro et al., 2009[69] Brazil Quality: Poor	108	Cross-sectional	Dyspareunia: Pain occurring during sexual intercourse	Self-report on form	49%
Pitts et al., 2008[70] Australia Quality: Poor	427	Cross-sectional	Dyspareunia: Pelvic pain during or in the 24 hours after intercourse	Self-reported during computer-assisted telephone interview	29%
Williams et al., 2004[64] US Quality: Poor	987	Cross-sectional	Deep dyspareunia: NR	NR	Organic[a]: 37% Functional[a]: 12% Mixed[a]: 11%
Grace et al., 2004[15] New Zealand Quality: Poor	214	Cross-sectional	Dyspareunia: Pelvic pain during or in the 24 hours after sexual intercourse	Self-reported on postal survey	41%
Johnson et al., 2004[71] New Zealand Quality: Poor	123	RCT	Deep dyspareunia: pain with sexual intercourse	History	60%
Chung et al., 2003[65] Korea Quality: Poor	106	Cross-sectional	Dyspareunia: NR	Symptoms reported by patient	15%
Ling et al., 1999[72] US Quality: Poor	85	RCT	Deep dyspareunia: NR	Physician evaluated	85%
Saravelos et al., 1995[75] UK Quality: Poor	123	Cross-sectional	Dyspareunia: NR	NR	63%
Peters et al., 1991[66] Netherlands Quality: Poor	106	RCT	Dyspareunia: NR	NR	71%

[a]The authors did not define the terms organic, functional, and mixed nor did they specify if these categories overlapped. N=number; NR=not reported; RCT=randomized controlled trial

Headache. Three studies from 2 unique populations reported the prevalence of headache[66, 68, 76]. In an RCT of surgical excision of endometriosis combined with raloxifene or placebo in 108 participants with CPP with and without endometriosis, 79 percent reported recurrent headaches[76]. Headaches were further classified using International Headache Society (IHS) Criteria. Among all of the 108 women, 67 percent had migraines (defined as 4 or 5 of the 5 major IHS criteria for migraines) and 12 percent had non-migraine headaches. The prevalence quality for this study was poor for headache and good for migraine.[76]

In an RCT of routine diagnostic laparoscopy versus an integrated approach without routine laparoscopy, 62 percent of 106 women with pelvic pain had headache.[66] The definition of headache and method of diagnosis were not provided for this study, which was of poor quality.[66]

Interstitial cystitis/painful bladder syndrome. Two studies reported the prevalence of IC/PBS. In a cross-sectional study of 175 consecutive women at a CPP clinic examining the nature and number of pain diagnoses, 35 percent had IC, defined as a positive response to alkalinized lidocaine bladder instillation or a previous diagnosis of IC from cystoscopy with hydrodistention.[77] This study was of good quality. In a prospective case series of 162 women with CPP who underwent laparoscopy and cystoscopy, 82 percent had IC defined as greater than 10 glomerulations per quadrant in at least 3 of 4 quadrants.[78] This study was of fair quality.

Irritable bowel syndrome. Ten studies reported the prevalence of IBS.[13-15, 62-64, 67, 77, 79, 80] Two studies with an overlapping population[14, 15] are reported separately because they used different methods of determining if the women had IBS.

As shown in Table 8, 5 studies used the Rome I or II criteria for diagnosis of IBS and reported prevalence rates of 24 percent to 39 percent (unadjusted mean 34 percent, median 35 percent).[13, 14, 64, 77, 79] It is possible that some or all of the women in 2 of these studies[64, 79] are the same because they are from the same clinic during the same time period; however, it is impossible to determine the extent of overlap. Three of these studies[13, 64, 77] were of good quality, and 2[14, 79] were of fair quality.

Five studies[13, 15, 62, 63, 80] reported IBS prevalence using methods other than the Rome criteria. In 2 studies, one of good quality[13] and one of fair quality,[15] women with CPP not exclusively related to menses or sexual intercourse, who had consulted a medical practitioner, self-reported diagnoses they were given. Rates were 26 percent among 149 women who responded to a postal survey in New Zealand,[15] and 20 percent among 237 women who responded to a postal survey in the United Kingdom.[13] One of these studies[13] also reported the percentage of women who met the Rome criteria for IBS, and those results are presented in Table KQ1-2.

The remaining 3 studies[62, 63, 81] were all of poor quality. A prospective cohort study of 370 women evaluated at a pelvic pain clinic reported 37 percent of women had a clinical diagnosis of IBS, defined as the physician indicating the diagnosis was definite or probable.[62] It is possible that some of the women in this study[62] are the same as women in 2 of the studies that used Rome criteria[64, 79] because they are from the same clinic during the same time period; however, it is impossible to determine the extent of overlap. Two studies reported prevalence rates for IBS but did not provide any information about how the diagnosis was made. One of these was an RCT of gabapentin and amitriptyline for CPP among 56 women, of whom 25 percent were reported to have IBS.[63] The other was a prospective case series of 106 women with CPP admitted for inpatient psychosomatic treatment, and 1 percent were reported to have IBS.[80]

Table 8. Prevalence of irritable bowel syndrome in women with noncyclic chronic pelvic pain

Author, Year Country Quality	N	Study Design	Diagnostic Criteria	Prevalence
Fenton et al., 2008[77] US Quality: Good	175	Cross-sectional	Rome II criteria	24%
Grace et al., 2006[14] New Zealand Quality: Fair	286	Cross-sectional	Rome I criteria	37%
Tu et al., 2006[79 a] US Quality: Fair	987	Cross-sectional	Rome I criteria	35%
Williams et al., 2004[64a] US Quality: Good	987	Cross-sectional	Rome I criteria	35%
Zondervan et al., 2001[13] UK Quality: Good	479	Cross-sectional	Rome I criteria	39%

[a]It is possible that some or all of the women in these 2 studies are the same because they are from the same clinic during the same time period; however, it is impossible to determine the extent of overlap. N=number

Sexual dysfunction. In addition to generalized sexual dysfunction, multiple specific forms of sexual dysfunction were reported including vaginismus, sexual pain disorder, postcoital pain, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and anorgasmia, and limits on sexual activity. Five studies addressed one or more of these forms of sexual dysfunction. One of these was of fair quality.[82] The remaining 4 studies were all of poor quality.[15, 62, 64, 66] See also the section on dyspareunia above.

Generalized sexual dysfunction. A cross-sectional study of fair quality about sexual dysfunction that included 112 women with CPP used the international classification of female sexual dysfunction (FSD)[82] of 4 FSD disorders to classify responses to general assessment questions designed to investigate women's sexual function. Among the 112 women, 70 percent had one or more of the 4 types of female sexual dysfunction (desire, arousal, orgasmic, and sexual pain disorders.).[82] In a prospective cohort of 370 women evaluated at a pelvic pain clinic, 76 percent had sexual dysfunction defined as "painful intercourse, decreased frequency, or decreased pleasure resulting from pain."[62] This study was of poor quality.

Hypoactive sexual desire disorder. A cross-sectional study about sexual dysfunction that included 112 women with CPP used the international classification of FSD disorders to classify responses to general assessment questions designed to investigate women's sexual function. Of the 78 women with CPP who had FSD, 54 percent had hypoactive sexual desire disorder.[82] The percentage of all of the women with CPP who had hypoactive sexual desire disorder is not reported.

Limits on sexual activity. A New Zealand postal survey about women's health included the open-ended question "Does your pelvic pain affect what you can or cannot do? If so, please describe." In response to this question, 6 percent of 286 women with CPP said they were "limited in sexual activity."[15]

Orgasmic disorder and anorgasmia. A cross-sectional study about sexual dysfunction that included 112 women with CPP used the international classification of FSD disorders to classify responses to general assessment questions designed to investigate women's sexual function. Of the 78 women with CPP who had FSD, 22 percent had orgasmic disorder.[82] The percentage of all of the women with CPP who had orgasmic disorder is not reported.

In an RCT of routine diagnostic laparoscopy versus an integrated approach without routine laparoscopy in 106 women with pelvic pain, 42 percent had anorgasmia.[66] The definition of anorgasmia (anorgasmy) and method of diagnosis were not provided.

Postcoital pain. In an RCT of routine diagnostic laparoscopy versus an integrated approach without routine laparoscopy in 106 women with pelvic pain, 27 percent had postcoital pain.[66] The method of diagnosis and parameters for how long the pain lasted were not provided.

Sexual Arousal Disorder. A cross-sectional study about sexual dysfunction that included 112 women with CPP used the international classification of FSD disorders to classify responses to general assessment questions designed to investigate women's sexual function. Of the 78 women with CPP who had FSD, 33 percent had sexual arousal disorder.[82] The percentage of all of the women with CPP who had sexual arousal disorder is not reported.

Sexual pain disorder. A cross-sectional study about sexual dysfunction that included 112 women with CPP used the international classification of FSD disorders to classify responses to general assessment questions designed to investigate women's sexual function. Of the 78 women with CPP who had FSD, 74 percent had sexual pain disorder.[82] The percentage of all of the women with CPP who had sexual pain disorder is not reported.

Vaginismus. Two studies, one prospective cohort and one cross-sectional, reported prevalence of vaginismus.[62, 64] The studies did not define vaginismus and relied on a clinical diagnosis defined as a physician indication that vaginismus was definite or probable. The rate of vaginismus was 5 percent in both studies.

Vulvodynia. Two studies of poor quality reported prevalence rates of vulvodynia. In a cross-sectional study of 175 consecutive women at a CPP clinic examining the nature and number of pain diagnoses, 5 percent had vulvodynia defined as point tenderness of the vulva including the introitus.[77]In a prospective cohort study of 370 women evaluated at a pelvic pain clinic, 7 percent had a clinical diagnosis of vestibulitis.[62] Clinical diagnosis was defined as a physician indicating the diagnosis was definite or probable, and vestibulitis was not defined.

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?

This section presents the results of our literature search and findings about outcomes of surgical interventions for the treatment of CPP. The surgical approaches represented in the literature meeting our criteria included diagnostic laparoscopy and laparotomy, hysterectomy, adhesiolysis of intraabdominal and pelvic adhesions, laparoscopic utero-sacral nerve ablation (LUNA), and utero-sacral ligament resection.

Overview of the literature

We identified 7 studies addressing surgical approaches; 5 were RCTs conducted in Europe or New Zealand, and 2 were prospective cohort studies conducted in the US. We rated one study as good[83], one as fair,[49], and 5 as poor quality.[52, 62, 66, 71, 84] Three studies compared surgical to nonsurgical or medical approaches for CPP treatment.[52, 62, 66] Three studies compared an active surgical technique, either LUNA or adhesiolysis, to surgical control (diagnostic laparoscopy).[49, 71, 83] One study directly compared 2 surgical techniques (LUNA vs. utero-sacral ligament resection).[84]

All studies provided definitions for CPP, although few generalizations can be drawn given the heterogeneity of definitions. All studies accepted patient self-report of pelvic pain or noncyclic pelvic pain as the principal determinant. Only one study specified a minimum degree of severity for pain as a definition component: ≥80 mm on 100 cm visual analog scale (VAS).[84] Three studies incorporated anatomic location in the definition: "midline,"[84] within or below the anterior iliac crests,[49] or abdomen below the umbilicus, pelvic organs, lower back, vulva, or vagina.[62] All but one stipulated a duration of greater than 6 months for chronicity, with one RCT allowing a duration of greater than 3 months.[66] One study limited the CPP definition to pelvic pain "unresponsive to common medical treatment."[84]

Key Points

- Of 7 studies addressing KQ2, one was assessed as good, one as fair, and 5 as poor quality.
- While surgical and nonsurgical approaches to treating CPP both improved pain status, neither was more effective when directly compared in 3 studies.
- Laparoscopic lysis of adhesions (with lysis of adhesions limited to those stricturing a bowel loop and a dilated lumen during diagnostic laparoscopy) did not further improve pain scores over diagnostic laparoscopy alone.
- LUNA was no more effective in improving pain status than diagnostic laparoscopy alone or utero-sacral ligament resection.

Detailed Analysis

Five RCTs addressed surgical approaches (Table 9). Among studies comparing active surgical techniques to diagnostic laparoscopy, a good quality RCT evaluated laparoscopic lysis of intraabdominal adhesions and randomly assigned patients with visually confirmed abdominal adhesions to either adhesiolysis (n = 51) or no adhesiolysis (n = 47) at the time of diagnostic laparoscopy.[83] The study included both men and women; however, over 80 percent of participants were female. The study does not present data for female participants only.

The potential effects of diagnostic laparoscopy in women with CPP have not been fully studied. Improvements following post-diagnostic laparoscopy have been reported but whether these improvements are "real" or "placebo" remains to be determined. Among studies using diagnostic laparoscopy as the comparator to an active intervention, diagnostic laparoscopy was used primarily as a diagnostic tool to try to identify potential pathologic explanations for CPP, and patients were randomized after the diagnostic laparoscopy. In these studies, patients were randomized at the time of surgery, after the diagnostic portion of laparoscopy, to receive additional treatment intervention or not.

After 12 months of followup, both the laparoscopic adhesiolysis group and the diagnostic laparoscopy group reported decreases in 100mm VAS pain scores; however, there was no difference in pain reduction between the 2 groups (p=0.63). The study was powered to measure a difference in the VAS of 35 percent between groups. The mean reduction in the VAS score was approximately 25 to 30 percent for both groups.[83]Quality of life (QOL), as assessed using the Medical Outcomes Study SF-36 instrument, improved in both groups with no significant differences between groups (p=0.84). The study did not evaluate functional status or patient satisfaction.

Two RCTs compared LUNA to diagnostic laparoscopy alone.[49, 71] One of these RCTs was of fair quality study and compared 185 patients with CPP randomized to receive LUNA to 185 patients randomized to receive no additional intervention at the time of diagnostic laparoscopy.[49] Pain scores as measured on a 10cmVAS for worst pain level (mean difference in VAS (cm) = -0.02; 95 percent CI [-0.61, 0.65]) or for noncyclic pain(mean difference in VAS (cm) = 0.17; 95 percent CI [-0.4, 0.74]) were not significantly different between groups. There were also no differences in pain scores between treatment groups when analyzed according to pre-determined subsets, including parity (nulliparous, parous), pathology (none, any, endometriosis), or site of pain (central, not central). Using the EuroQOL indices of quality of life, the EQ-5D and EQ-VAS, the authors compared mean differences in scores between the 2 treatment groups and demonstrated no differences in either measure: For EQ-5D, the mean difference was 0.03 (95 percent CI, -0.03 to 0.09), and for EQ-VAS, the mean difference was -0.78 (95 percent CI, -3.9 to 5.4). The study did not assess functional status or patient satisfaction as outcomes.[49]

The second of the 2 RCTs was a poor quality study comparing LUNA with diagnostic laparoscopy.[71] Investigators randomly assigned women with CPP at diagnostic laparoscopy to receive either LUNA or no additional treatment and sub-classified participants according to the presence of endometriosis. When patients with no endometriosis receiving LUNA (n= 18) were compared to those not receiving LUNA (n = 32) after 12 months of follow-up, there were no statistical differences in median change in 10cm VAS score for nonmenstrual pelvic pain (p= 0.34) nor in numbers of patients with a greater than 50 percent reduction in VAS score (p= 0.8). Similarly, in patients with endometriosis, there were no differences between patients receiving LUNA (n=26) and those not receiving LUNA (n=30) in change in VAS score for pelvic pain (p= 0.58) or numbers of patients with more than 50 percent reduction in VAS score (p= 0.78).

The authors also reported that satisfaction rates in patients with or without endometriosis that receive either LUNA or diagnostic laparoscopy alone did significantly differ; however, the paper provided no description for how satisfaction was assessed or what measure was used. The study did not assess functional status.[71]

In the only study included in this section of the review to actively compare surgical treatments, Palomba et al. randomly assigned 80 patients with CPP to either LUNA or vaginal utero-sacral ligament resection.[84] After 12 months of follow-up, 36 patients receiving LUNA and 38 patients receiving ligament resection were available for evaluation. Both groups reported improvements in pain severity on 100mm VAS score; however, there was no difference in pain severity between the 2 groups (p= 0.063). The study reported equivalent rates of cure (defined as complete relief of pain or residual CPP not requiring treatment) for both treatment arms (RR = 0.9, 95 percent CI [0.78 to 1.33]). The study did not address functional status, patient satisfaction or quality of life as outcomes after surgery.

One poor quality study included women with CPP for whom the initial gynecologic history and physical and psychiatric evaluation did not result in a high index of suspicion for a particular

etiology.[66] The women were randomized to either a "standard approach" that included laparoscopy, or an "integrated approach" that included somatic or behavioral therapies. Following the laparoscopy, the authors do not report how many of the 49 patients in this group received any subsequent interventions such as physiotherapy or behavioral therapy.

The 57 patients in the integrated approach group received physiotherapy and "equal attention was devoted to possible organic, psychological, dietary, and environmental causes of the pain," meaning they may have received medical treatments, diet and nutrition advice, or psychosocial therapy. Of the 57 patients in the integrated approach group, 5 eventually underwent a surgical intervention. In this small study population of 57 participants, of whom over 90 percent had undergone prior laparotomy for CPP, performing a laparoscopy as the next step was not as helpful for improving the "general pain experience" or the "disturbance of daily activities" as enrolling the patient in a multidisciplinary program that included physiotherapy. Improvement in general pain experience was reported by 75 percent in the integrated approach group and 41 percent in the surgical approach group. Improvement in disturbance of daily activities was reported by 68 percent in the integral approach group and 37 percent in the surgical approach group, but the authors do not report how improvements in pain experience were determined. Objective multidimensional McGill pain scores were not different between the 2 groups at the 1-year evaluation.[66] There were no differences between treatment arms in improvement in McGill scores after 12 months of treatment ($p= 0.38$), although "improvement" in McGill scores was not explicitly defined.

Two prospective cohort studies addressed surgical approaches for treating CPP; both studies were poor quality. One study involved participants from tertiary referral centers in the United States and compared medical to surgery therapy for CPP.[62] One hundred eighty one patients receiving nonsurgical or medical therapy, including pharmaceutical therapy (with opioid and nonopioid analgesics, antidepressants, anxiolytics, antineuropathics, sedatives, hormones or anti-inflammatories), physical therapy, psychotherapy or combinations thereof, were compared to 189 patients receiving surgical therapy (including diagnostic laparoscopy, adhesiolysis, endometrial ablation, oophorectomy, hysterectomy, and utero-sacral ablation). After 12 months of follow-up, both groups reported significantly lower scores on the McGill Pain Questionnaire (both $p < 0.001$) from baseline, although the improvement was similar in both groups (OR = 1.2, 95 percent CI [0.8, 1.6]). There were no significant differences in change of pain status between the 2 groups, with similar numbers of patients reporting worsened pain (OR = 0.9, 95 percent CI [0.5-1.5]), no change (OR = 1.1, 95 percent CI [0.7-1.7]), improvement (OR = 0.8, 95 percent CI [0.4-1.6]), or resolution of pain (OR = 0.9, 95 percent CI [0.5-1.5]. The study did not assess functional status, patient satisfaction with care, and quality of life.

A poor quality cohort study, the Maine Women's Health Study, addressed nonsurgical management of participants with CPP who had undergone prior diagnostic laparoscopy and did not have endometriosis or any other condition that warranted a specific treatment.[52] The study reported on 12-month outcomes for 380 patients enrolled in a nonsurgical group compared to 311 patients undergoing hysterectomy in the original Maine Women's Health Study.[53] Patients included in the nonsurgical group were those with complete evaluations, including diagnostic laparoscopy, who elected nonsurgical management for leiomyomas, abnormal bleeding or CPP. Only 50 (13 percent) patients with a primary diagnosis of CPP were included in the nonsurgical group. Patients included in the hysterectomy group were those undergoing hysterectomy for non-malignant indications, including leiomyomas, abnormal bleeding, or CPP. Sixty-eight (22 percent) patients undergoing hysterectomy reported a primary diagnosis of CPP. The study also

included limited data on a subset of 71 women with CPP only, (without a primary indication of fibroid or abnormal bleeding or other) who underwent nonsurgical management.

Both the surgical and nonsurgical group demonstrated significant improvement in mean number of days with pain as determined by structured interview after 12 months of treatment. Those in the nonsurgical group reported a mean reduction of 7 days (from 16 to 9, $p < 0.001$), while those in the hysterectomy group reported a mean reduction of 18 days (from 19 to 1, $p < 0.001$). The study did not report comparisons between the 2 groups.

Functional status, assessed with a validated Activity Index questionnaire, improved in both groups compared to baseline after 12 months of treatment (both $p < 0.001$), although comparison between the 2 arms was not performed. Quality of life improvements were assessed via the Mental Health Index, General Health Index, Activity Index, and assessment of positive feelings about symptom status. For all these QOL measures, hysterectomy was associated with significant improvements at 12 months compared to baseline ($p < 0.001$ for all), while nonsurgical management was only associated with significant improvements in the Activity Index and positive feelings about symptom status ($p < 0.001$ for both).

The authors report that the likelihood of positive feelings about symptoms status at 1 year of follow-up was significantly increased for participants receiving hysterectomy compared with nonsurgical management (OR=10.45, adjusted for treatment type, age, fertility, parity, education, duration of symptoms, and initial severity of discomfort). Thirty percent of the 50 women with CPP who had nonsurgical management, who completed the 1-year follow-up and did not have a hysterectomy during that year, reported positive feelings about symptom relief, compared with 77 percent of 68 women with CPP who had hysterectomy. However, the decision about whether or not to have a hysterectomy was made by the woman and her physician prior to enrolment in the study. Therefore, the study reports that women who self-selected for hysterectomy as a treatment for CPP were more likely to be satisfied with their symptom status after one year than women who self-selected nonsurgical management as a treatment for CPP, with the proviso that the factors that influenced the decision about therapy were not studied.[52]

Table 9. Key outcomes of surgical interventions for noncyclic CPP

Author, Year, Country Quality	Comparison Groups, N	Outcomes
Adhesiolysis		
Swank et al., 2003[83], The Netherlands Quality: Good	**G1:** Adhesiolysis at diagnostic laparoscopy, 51 **G2:** No adhesiolysis at diagnostic laparoscopy, 47	• No significant differences in 100cm VAS pain score at 12 months between either group (P = 0.63)
Hysterectomy vs. nonsurgical therapy		
Carlson et al., 1994[52] U.S. Quality: Poor	**G1:** Nonsurgical management, 50 **G2:** Hysterectomy, 68	• Both groups demonstrated significant improvement in number of days with pain at 12 months: G1: 16 to 9 days, P < 0.001; G2: 19 to 1 day, P < 0.001 • Significant decreases in proportions of patients for whom pain was a problem at 12 months vs. baseline were reported for both groups (P < 0.001 for both)

Table 9. Key outcomes of surgical interventions for noncyclic CPP (continued)

Author, Year, Country Quality	Comparison Groups, N	Outcomes
LUNA vs. diagnostic laparoscopy		
Daniels, 2009[49], UK Quality: Fair	**G1:** LUNA at diagnostic laparoscopy, 185 **G2:** No LUNA at diagnostic laparoscopy, 185	• No significant difference between groups in 10cm VAS for noncyclic pain level at 12 months
Johnson, 2004[71], New Zealand Quality: Poor	**G1a:** LUNA at diagnostic laparoscopy, without endometriosis, 18 **G2a:** No LUNA at diagnostic laparoscopy, without endometriosis, 32 **G1b:** LUNA at diagnostic laparoscopy, with endometriosis, 26 **G2b:** No LUNA at diagnostic laparoscopy, with endometriosis, 30	• No significant differences in change from baseline of nonmenstrual pelvic pain score on 10-point VAS at 12 months between G1a vs. G2a (p = 0.34) or G1b vs. G2b (p = 0.58) • No significant differences in > 50% reduction of pain from baseline at 12 months on 10-point VAS between G1a vs. G2a (p = 0.80) or G1b vs. G2b (p = 1.0) • No significant differences in numbers of successful treatments at 12 months between G1a vs. G2a (p = 0.85) or G1b vs. G2b (p = 0.77)
LUNA vs. utero-sacral ligament resection		
Palomba, 2006[84], Italy Quality: Poor	**G1:** LUNA, 36 **G2:** Utero-sacral ligament resection, 38	• Comparable pain severity scores on 100mm VAS at 12 months reported for both groups (p = 0.063) • Relative risk of cure rates (complete relief of pain and CPP not requiring treatment) between G1 vs. G2 = 0.90 (95% CI: 0.78 – 1.33)
Surgical vs. nonsurgical therapy		
Lamvu et al., 2006[62], U.S. Quality: Poor	**G1:** Nonsurgical therapy, 181 **G2:** Surgical therapy, 189	• MPQ scores after 12 months of therapy were significantly lower in both groups (both p < 0.001), but not significantly different from each other (p = 0.165) • Overall odds of improvement in MPQ score for surgical vs. nonsurgical treatments were similar (OR = 1.2, 95% CI [0.8, 1.6] • Comparable numbers of patients in each group with worsened pain (OR = 0.9, 95% CI [0.5, 1.5]), no change in pain (OR = 1.1, 95% CI [0.7, 1.7]), improvement in pain (OR = 0.8, 95% CI [0.4, 1.6]), and resolution of pain (OR = 0.9, 95% CI [0.5, 1.5])
Peters et al., 1991[66], The Netherlands Quality: Poor	**G1:** Standard treatment approach, including routine diagnostic and/or therapeutic laparoscopy, 49 **G2:** Integrated treatment approach, without routine laparoscopy, 57	• No difference in numbers of patients with improvement in MPQ scores at 12 months between groups (p = 0.38) • Significant improvement in numbers of patients with improvement in relative disturbance of daily activities for those treated with integrated approach vs. standard approach (p < 0.01)

CPP= noncyclic chronic pelvic pain; G=group; OR= odds ratio; LUNA=laparoscopic utero-sacral nerve ablation; MPQ=McGill Pain Questionnaire; VAS=visual analog scale

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?

We sought evidence that surgical outcomes differed if the etiology of CPP was identified after surgical intervention. We searched for studies of surgical interventions for CPP that reported outcome measures of interest and which indentified at least 2 groups: those participants who had an etiology identified at the time of the surgical intervention or from surgical histopathology, and those participants who did not have an etiology identified at surgery or from pathology. Surgical approaches included in the literature meeting our criteria are described more fully in the KQ2 section of the report and included laparoscopy, laparoscopic lysis of adhesions, LUNA, and hysterectomy.

We did not identify any studies of surgical procedures in participants with CPP that reported outcomes separately for participants who had an etiology identified compared with those who did not have an etiology identified.

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?

Overview of the Literature

This section presents results of studies meeting our review criteria and addressing the effectiveness of nonsurgical (pharmacologic and nonpharmacologic) interventions for CPP and harms of such interventions. Sixteen studies meeting our criteria addressed nonsurgical approaches for CPP. Thirteen of these studies were RCTs, one study qualified as a nonrandomized trial, and 2 were prospective cohort studies (Table 10). Only one study was rated as high quality,[68, 76] 3 were fair quality,[72, 85, 86] and the balance were poor.[52, 62, 63, 66, 73, 74, 87-92] The few placebo-controlled studies[68, 72, 85] were consistently rated as higher quality.

Most RCTs investigated hormone-based treatments for CPP. One evaluated antineuropathic agents, and another the neuromuscular blocking agent, botulinum toxin A. Four RCTs examined nonpharmacologic therapies—pelvic floor physical therapy, photographic-enhanced counseling after surgery, pelvic ultrasonography plus counseling, and a standard versus integrated treatment approach. The nonrandomized trial also evaluated outcomes of hormone-based therapy while the cohort studies assessed nonsurgical compared with surgical approaches.

Eleven of the 16 studies were performed in Europe, with the remainder conducted in the United States and Australia. Most were conducted at academic institutions. The definition of CPP varied slightly between studies, with several studies not providing a clear definition at all. Most commonly, CPP was defined as moderate to severe pelvic pain for at least 6 months duration, unrelated to menstruation. However, among these studies, the duration ranged between 3 months and 2 years. The required severity of pain varied among studies, with some studies requiring a baseline score on a specified pain index/scale while others relied on patient report only. Several studies (n=8), especially those that trialed hormone-based therapies, also required patients to have a diagnosis of endometriosis. Other than those requiring a diagnosis of endometriosis, studies addressing KQ4 reported no consistent screening for other pain conditions or co-morbidities. A full gynecologic and obstetric history was also rarely reported.

Key Points

- Only one study met criteria for good quality; this study demonstrated that a selective estrogen receptor modulator (SERM), raloxifene, was associated with a faster return of endometriosis-associated pelvic pain.
- The majority of studies reviewed here are RCTs, most of which investigate hormone-based therapies.
- More often, studies compared active vs. active interventions; thus is it difficult to determine whether or not both arms are actually demonstrating placebo effect vs. treatment effect.
- There was limited reporting of a systematic evaluation of participants prior to randomization to ascertain the etiology of pelvic pain prior to treatment.
- Reporting of harms data was very limited among trials; among the placebo-controlled trials, harms were more frequent in the placebo arms.

Detailed Analysis

Hormonal therapies. Hormonal treatments for pelvic pain, with or without an underlying diagnosis of endometriosis, were the most common treatment studied. We identified 7 RCTs[68, 72-74, 76, 88-90] and one nonrandomized controlled trial[87] involving hormone-based therapies (Table 10). Six were conducted in Europe[73, 74, 87-90] and 2 in the United States[68, 72, 76] with 776 total participants. Two of these used placebo as the control,[68, 72] while the remainder compared 2 or more active interventions. These included combined estrogen/progesterone contraceptive agents, gonadotropin releasing hormone (GnRH)-analogues, a SERM, and progesterone injection.

Pain reduction was the primary pain-based outcome measured in all studies; however, many tools used to measure this outcome varied. Six studies used a 0-10 point VAS.[68, 72, 73, 87, 88, 90] One study[74] utilized a 10 cm VAS and one used a 100mm VAS.[89] In addition to a VAS, several studies evaluated participants with other pain scales including the McGill Pain Questionnaire, Biberoglu and Behrman scale, and SF-12 or 36. The lack of consistent outcome measures limited our ability to compare outcomes across studies.

One good quality study, one of the few to employ a placebo, evaluated a SERM, raloxifene, looking at its effect on pelvic pain in participants with biopsy-proven endometriosis.[68] Compared with placebo, those participants who received raloxifene experienced a return of pain significantly sooner after laparoscopy (OR, 2.81; 95 percent CI,1.41-6.19). The effect was so pronounced that the trial was stopped early.

Four studies investigated the effects of the GnRH-analogue leuprolide acetate on pelvic pain. In one fair quality, placebo-controlled study,[72] participants randomized to depot leuprolide had significantly greater improvement in pelvic pain scores at the end of 12 weeks of treatment, compared to those randomized to placebo ($p<0.001$). These participants all had clinically suspected endometriosis. The other 3 studies were poor quality and compared leuprolide acetate to another active treatment. When compared to gestrinone, a similar GnRH-analogue with mild progestogenic and androgenic effects, both treatment groups experienced significant reduction in pain scores during the treatment period.[74] However, the gestrinone group showed overall lower pain scores at the end of follow-up, compared to leuprolide recipients. The third study evaluated add-back therapy in participants receiving leuprolide acetate for the treatment of endometriosis-associated pain.[88] Participants were randomized to leuprolide alone, leuprolide plus daily estradiol and norethindrone, or a daily estroprogestin alone. Participants treated with leuprolide

(either with or without add-back therapy) had significantly greater reduction in pain scores compared to those treated with the estroprogestin alone ($p<0.01$). Those with add-back therapy reported better quality-of-life. The fourth study compared treatment with estroprogestin alone for 12 months to treatment with a GnRH agonist for 4 months followed by with estroprogestin for 8 months for the treatment of endometriosis-associated pain.[90] While both arms were effective in the treatment of pain, there was no difference between arms.

Two poor quality studies evaluated monophasic oral contraceptive pills (OCP), both for the treatment of pain associated with endometriosis. The first study[89] randomized participants to depot medroxyprogesterone or OCP plus low dose danazol. Both groups reported significant improvement in pain scores, compared to baseline, with no significant between-group difference. In the second study, OCPs were compared to goserelin, another GnRH-analogue.[73] During the treatment period, both groups experienced similar reduction of pain, but then had similar return to baseline pain levels once treatment was stopped. There was no significant between-group difference.

The final hormonal intervention study, also of poor quality, compared 2 contraceptive delivery methods—the contraceptive vaginal ring (ethinyl estradiol/etonogestrel) and the transdermal patch (ethinyl estradiol/norelgestromin)—for the treatment of endometriosis-associated pain.[87] In this nonrandomized study, participants chose their preferred delivery method. The primary outcome of this study was treatment satisfaction, and the study reported no difference between groups in satisfaction with treatment. The study did not report data for the secondary outcome of nonmenstrual pain.

Table 10. Key outcomes of hormonal therapies for noncyclic CPP

Author, Year, Country Quality	Intervention, N at enrollment (N at follow-up)	Last outcome assessment post treatment day 1	Key findings
Vercellini et al., 2010,[87] Italy Quality: Poor	**G1**: Vaginal ring (15 mcg ethinyl E and 120 mcg etonogestrel/day), 72 (32) **G2**: Transdermal patch (20 mcg ethinyl E and 150 mcg norelgestromin/day), 23 (19)	At end of 12 months of treatment	• Pain symptoms were reduced significantly in both groups, with no significant difference between groups. • No differences in noncyclic pain outcomes in those with or without rectovaginal lesions. Patients who chose the patch were more likely to drop out of the study compared with those who chose the ring (RR, 1.7; 95% CI, 1.27-2.28) • Irregular bleeding was a common side effect in both groups in those who attempted continuous use (ring 46%, patch 42%) • Ring users were more likely to be satisfied with treatment
Stratton et al., 2008,[68] US Quality: Good	**G1:** Raloxifene, 180 mg/day, 47 (38) **G2:** Placebo, 46 (35)	12 months after patient completed 6 months of treatment	• Raloxifene group experienced quicker return of pain ($p=0.03$) and required repeat surgery sooner than placebo group ($p=0.016$) • Presence of biopsy-proven endometriosis was not significantly associated with return of pain • Study was terminated early due to negative effect

Table 10. Key outcomes of hormonal therapies for noncyclic CPP (continued)

Author, Year, Country Quality	Intervention, N at enrollment (N at follow-up)	Last outcome assessment post treatment day 1	Key findings
Zupi, et al., 2004,[88] Italy Quality: Poor	**G1:** GnRH-analogue (leuprolide acetate 11.25 mg IM every 3 months), 46 (NR) **G2:** GnRH-analogue (leuprolide acetate 11.25 mg IM every 3 months) and transdermal E2 25 mcg/day + norethindrone 5 mg/day, 44 (NR) **G3:** Estroprogestin alone (ethinyl E2 30 mcg/day + gestodene 0.75 mg/day), 43 (NR)	6 months after patient completed 12 months of treatment	• Patients treated with GnRH-analogue (either with or without add-back therapy) had significantly greater reduction in pain scores compared with those treated with oral contraceptive therapy (p<0.01) • Significant loss of bone mineral density noted in both GnRH-analogue groups, but less so in the group given add-back therapy • Patients treated with GnRH-analogue plus add-back therapy reported overall better quality of life than those in the other 2 groups
Parazzini et al., 2000[90] Italy Quality: Poor	**G1:** estroprogestin (gestodene/ethinyl estradiol) 0.75 mg/0.03 mg daily for 12 months, 46 (NR) **G2:** GnRH agonist (triptorelin) 3.75 mg IM for 4 months, followed by estroprogestin daily for 8 months, 49 (NR)	12 months	• Significant improvement in pain scores over 12 months of treatment in both groups • No statistically significant difference between groups in overall pain improvement • Endometriosis stage had no significant effect on pain status
Ling et al., 1999,[72] US Quality: Fair	**G1:** Depot leuprolide, 3.75 mg IM every 4 weeks, 50 (49) **G2:** Placebo, 50 (46)	At end of 12 weeks of treatment	• Leuprolide group had significant reduction in all pain scores compared with placebo (p<0.001) • Majority of patients in both groups had laparoscopically-confirmed endometriosis after 12 weeks of treatment (leuprolide 78%, placebo 87%) • Most commonly-reported statistically significant harms in the treatment group were hot flushes (80%), insomnia (40%), and enlarged abdomen (percentage not reported) (p ≤ 0.50)

Table 10. Key outcomes of hormonal therapies for noncyclic CPP (continued)

Author, Year, Country Quality	Intervention, N at enrollment (N at follow-up)	Last outcome assessment post treatment day 1	Key findings
Gestrinone Italian Study Group, 1996,[74] Italy Quality: Poor	**G1:** Gestrinone, 2.5 mg/2x week, 27 (17) **G2:** Leuprolide acetate, 3.75 mg IM every 4 weeks, 28 (17)	6 months after patient completed 6 months of treatment	• Both groups experienced significant reduction in pain during the treatment period • Gestrinone group showed overall lower pain scores at the end of follow-up, compared with the leuprolide group • Recurrence of moderate-severe pain observed less frequently in the gestrinone group, compared to the leuprolide group (OR, 0.12; 95% CI, 0.02-0.69) • Nonsignificant increase in bone mineral density in the gestrinone group and a statistically significant decrease (-3.04% ± 4.77%) in the leuprolide group
Vercellini et al., 1996,[89] Italy Quality: Poor	**G1:** Depot medroxy-progesterone acetate, 150 mg IM every 90 days, 36 (36) **G2:** Monophasic OCPs (ethinyl estradiol 0.02 mg/desogestrel 0.15 mg) with danazol 50 mg), 32 (32)	At the end of 12 months of treatment.	• Significant improvements in pain scores noted in both treatment groups without significant between-group difference • 72.5% of depot medroxyprogesterone patients were either satisfied or very satisfied with treatment, compared to 57.5% of OCP users • Larger proportion of depot medroxyprogesterone patients experienced side effects during the treatment period
Vercellini et al., 1993,[73] Italy Quality: Poor	**G1:** Goserelin, 3.6 mg every 28 days, 29 (26) **G2:** Monophasic OCP with ethinyl estradiol 0.02 mg/day, 28 (24)	6 months after patient completed 6 months of treatment	• Both groups experienced improvement in pain during treatment without significant differences between groups • At end of follow-up, both groups experienced similar return to baseline pain levels • Symptoms recurred in most patients 6 months after treatment end

CI=confidence interval; CPP=noncyclic chronic pelvic pain; G=group; GnRH=gonadotropin releasing hormone; IM=by mouth; mg=milligram; OCP=oral contraceptive pills; OR=odds ratio; N=number; NR=not reported; RR=relative risk

Other pharmacologic therapies. The nonhormonal treatments evaluated include the neuromuscular-blocking agent botulinum toxin A[85] and anti-neuropathic agents gabapentin and amitriptyline.[63] In a fair quality, placebo-controlled study, women with 2 years of pelvic pain due to pelvic floor spasm were randomized to injection of the pelvic floor muscles with botulinum toxin A or saline.[85] Pain scores, followed for 6 months after injection, were significantly improved in the botulinum group compared to placebo (p=0.009). However, both groups had significantly decreased pelvic floor pressures after 6 months with no significant between-group difference.

In a poor quality anti-neuropathic study,[63] participants were randomized to one of 3 arms: gabapentin daily, amitriptyline daily, or gabapentin plus amitriptyline daily. Each group demonstrated significant improvement in pain from baseline scores; however, pain reduction was significantly greater in participants who received gabapentin (either with or without amitriptyline). Table 11 summarizes key outcomes for these nonhormonal therapies.

Table 11. Key outcomes of nonhormonal pharmacologic treatments for noncyclic CPP

Author, Year, Country Quality	Intervention, N at enrollment (N at follow-up)	Last outcome assessment post treatment day 1	Key findings
Abbot et al., 2006,[85] Australia Quality: Fair	**G1:** Botulinum toxin type A, 80 units, 30 (29) **G2:** Placebo (saline), 30 (28)	6 months after injection	• Botulinum toxin treatment group showed significant improvement in nonmenstrual pelvic pain scores (p=0.009); the placebo group did not • Significantly decreased pelvic floor pressures from baseline in both treatment groups (p<0.001, p=0.003) • Notable events/serious complications occurred in 4 women in the botulinum toxin group
Sator-Katzenschlager et al., 2005,[63] Austria Quality: Poor	**G1:** Gabapentin, maximum 3600 mg/day, 20 (17) **G2:** Amitriptyline, maximum 150 mg/day, 20 (17) **G3:** Gabapentin + amitriptyline, 16 (15)	At the end of 24 months of treatment	• All patients experienced significant pain relief during treatment and at the end of treatment, compared with baseline scores • Between groups, pain reduction was significantly greater in those who received gabapentin alone or gabapentin/amitriptyline combination compared with those who received amitriptyline alone • Incidence of dose-limiting side effects was lower in the gabapentin group, compared to the other 2 groups • No significant difference between groups in the incidence of severe side effects (those requiring discontinuation of treatment)

CPP=noncyclic chronic pelvic pain; G=group; mg=milligram; N=number

Nonpharmacologic therapies. Four trials addressed nonpharmacologic treatments for CPP (Table 12). The first of these was the only one to evaluate pelvic floor physical therapy, described as "distension of painful pelvic structures" as a treatment for pelvic pain.[86] In this fair quality study the control group received counseling only. Participants were evaluated at baseline and 2 to 3 weeks after treatment. Those randomized to pelvic floor distention showed significant improvement in pain scores compared to controls (OR, 18.37; 95 percent CI 3.39-99.64).

Two studies, both of poor quality, addressed practice-based treatment approaches and their effectiveness for overall pain outcomes. The first looked at post-operative counseling after diagnostic laparoscopy, and the effect of showing operative photos from the surgery while discussing findings.[91] The addition of photos to counseling had no effect on overall pain scores.

The second study[66]sought to determine if an integrated treatment approach to pelvic pain (promoting equal attention to organic, psychological, dietary, and environmental causes of pain) was more effective than the standard approach (excluding organic causes before looking

elsewhere) in patients in whom the initial gynecologic history and physical and psychiatric evaluation at the specialty clinic did not result in a high index of suspicion for a particular etiology for CPP. Participants randomized to the integrated approach showed greater improvement in scores in 3 areas: "general pain experience" ($p<0.01$), "disturbance of daily activities" ($p<0.01$), and "associated symptoms" ($p<0.01$). However, there was no significant difference in improvement in McGill pain scores between the integrated and standard approaches.

A fourth poor quality study randomized 100 patients with CPP after a negative laparoscopy to a session of ultrasound and counseling or a "wait and see" approach.[92] Participants had similar pain duration, McGill pain scores, and Hospital Anxiety and Depression scale scores at baseline. The study reported that performing an interactive pelvic and transvaginal ultrasound with demonstration, education, reassurance that the findings were normal, and counseling resulted in resolution of pain for 12/46 patients, compared with 4/44 patients in the "wait and see" group.

Table 12. Key outcomes of nonpharmacologic treatments for noncyclic CPP

Author, Year, Country Quality	Intervention, N at enrollment (N at follow-up)	Last outcome assessment post treatment day 1	Key findings
Heyman et al., 2006,[86] Sweden Quality: Fair	**G1:** Distension of the pelvic floor muscles and joint between the coccyx and rectum, 25 (22) **G2:** Counseling, 25 (22)	2-3 weeks after treatment	• Pelvic floor treatment group showed significant improvement in pain scores compared to the counseling group (OR, 18.37; 95% CI, 3.39-99.64)
Onwude et al., 2004,[91] UK Quality: Poor	**G1:** Photographic reinforcement , 109 (53) **G2:** No reinforcement, 124 (62)	6 months after treatment	• No significant difference in changes in pain scores between groups
Ghaly, 1994[92] Scotland Quality: Poor	**G1:** Pelvic ultrasonography plus counseling, 50 (46) **G2:** Expectant management, 50 (44)	4-9 months	• Greater improvement in pain scores in the ultrasound group ($P<0.01$) • Pain reported as resolved in 12/46 participants in ultrasonography group and 1/44 in the expectant management group

Table 12. Key outcomes of nonpharmacologic treatments for noncyclic CPP (continued)

Author, Year, Country Quality	Intervention, N at enrollment (N at follow-up)	Last outcome assessment post treatment day 1	Key findings
Peters et al., 1991,[66] Netherlands Quality: Poor	**G1:** Standard treatment (exclusion of organic causes of pain and routine laparoscopy before attention devoted to treating other causes, 49 (49) **G2:** Integrated approach (equal attention devoted to organic, psychological, dietary, and environmental causes of pain, including consultation with physiotherapist; laparoscopy not routinely performed, 57 (57)	Approximately 12 months after patient completed treatment	• Integrated approach significantly associated with pain improvement in 3 areas: general pain experience (p<0.01), disturbance of daily activities (p<0.01), and associated symptoms (p<0.01) • No significant between-group difference in McGill scores

CI=confidence interval; G=group; N=number; OR=odds ratio

Medical vs. surgical management. Two poor quality prospective cohort studies addressed nonsurgical approaches (Table 13).[52, 62] In one study, 370 patients in a pelvic pain clinic were followed for a year after treatment either by medical or surgical intervention.[62] The choice of treatment was provider-based and solely derived by clinical interaction. Participants were asked to complete baseline questionnaires regarding general medical information, history of abuse, depression screening, and pain assessment. The pain and depression assessments were repeated after one year. Groups were divided into those who received surgical treatment (with or without medical treatment) and medical treatment alone. Though the patient populations and treatment algorithms were highly varied, baseline characteristics were fairly evenly distributed. At the end of one year, improvement in pain was similar in both groups (OR 1.2, 95 percent CI 0.8-1.6).

In the Maine Women's Health Study,[52] patients with leiomyomas, abnormal bleeding, or pelvic pain were recruited from private obstetrics and gynecology practices to determine improvement in these conditions when treated with either medical options or hysterectomy. Over the course of their treatment, 118 patients were followed by questionnaire administered at baseline, 3, 6, and 12 months, and included demographic information as well as indices for quality-of-life, functionality, and pain severity. While both treatment groups experienced improvement in pain severity and quality-of-life, the hysterectomy group showed an even greater degree of change.

Table 13. Key outcomes of studies comparing nonsurgical with surgical treatment of CPP

Author, Year, Country Quality	Intervention, N at enrollment (N at follow-up)	Last outcome assessment post treatment day 1	Key findings
Lamvu, et al., 2006[62] US Quality: Poor	**G1:** medical treatment, NR (181) **G2:** surgical treatment, NR (189)	At end of 12 months of treatment	• Improvement in pain scores was similar in both groups • The odds of improvement in both groups was 1.2 (95% CI 0.8-1.6) • Improvement in depression scores was also similar in both groups after one year
Carlson, et al., 1994[52] US Quality: Poor	**G1:** nonsurgical management, (N not clearly reported) **G2:** hysterectomy, (N not clearly reported)	1 year after initiation of treatment	• A substantial proportion (25%) of patients treated medically for abnormal bleeding or pelvic pain will later choose hysterectomy • The odds of positive feelings about pelvic pain symptoms at 1 year were 10.45 (p=0.0001) for hysterectomy compared with nonsurgical management

CI=confidence interval; CPP=noncyclic chronic pelvic pain; N=number; NR=not reported; OR=odds ratio

Harms of nonsurgical interventions. Among the few placebo-controlled studies addressing nonsurgical approaches to treating CPP,[68, 72, 85] reported harms included depression, amenorrhea, sleep changes, hot flushes, and headache (Table 14). Harms were more frequent in placebo arms compared with either active GnRH agonist or the SERM raloxifene. The numbers of adverse events reported in a placebo (saline) versus botulinum toxin group were roughly equivalent.[85]

Additional harms reported in non-placebo controlled studies included spotting/breakthrough bleeding, changes in libido, vaginal dryness, mood changes, breast tenderness, weight gain, nausea and vomiting, dizziness, skin manifestations, and joint pain.

Table 14. Nonsurgical harms[a] reported in placebo-controlled studies

Reported event	Placebo	GnRH agonists	SERM
	Range of % of participants with adverse event (number of studies reporting event)		
Amenorrhea	4 (1)	98 (1)	NR
Depression	22 (1)	NR	NR
Headache	20-22 (2)	NR	21 (1)
Hot flushes	26 (1)	80 (1)	NR

Table 14. Nonsurgical harms[a] reported in placebo-controlled studies (continued)

Reported event	Placebo	GnRH agonists	SERM
	Range of % of participants with adverse event (number of studies reporting event)		
Ovarian cyst	11 (1)	NR	17 (1)
Reduction/discontinuation of study drug	49 (1)	NR	32 (1)
Sleep changes	NR	40 (1)	NR

GnRH= gonadotropin releasing hormone; NR=not reported; SERM=selective estrogen receptor modulator
[a]Studies report harms for all participants only (vs. only those participants with noncyclic pain)
NOTE: An RCT of botulinum toxin A compared with placebo[85] did not allow for calculation of percentages but reported total events per group (botulinum toxin/placebo): headache (20/20), cold/flu symptoms (33/42), pelvic/back pain (26/30), gastroenterological symptoms (11/8)

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)?

We sought evidence for choosing one intervention over another to treat persistent or recurrent CPP after an initial intervention failed to achieve the target outcome(s). We did not identify any comparative studies of interventions explicitly noting prior failed interventions and addressing this question.

Summary and Discussion

In this section, we summarize our findings about therapies for women with noncyclic chronic pelvic pain (CPP). We provide an overview of the state of the literature and outcomes for each key question (KQ), detail the strength of evidence for the impact of each major intervention on relevant outcomes, and describe major issues and gaps in the current body of evidence.

State of the Literature

Despite a high reported prevalence for noncyclic CPP,[8] little research assessing therapies exists. While there are many publications regarding pelvic pain, there are relatively few addressing noncyclic CPP, and of those, few were high quality. Seventeen of 33 studies meeting our criteria were randomized controlled trials (RCTs); however, only 3 were placebo controlled.[68, 72, 85] This lack of placebo comparison detracts from the active head-to-head trials because no initial validation of effect has been made.

Some surgical studies compared a surgical approach to diagnostic laparoscopy or compared surgical to nonsurgical management. In the nonsurgical literature, most studies compared active agents to active agents, and a number addressed hormonal therapies for endometriosis-associated CPP. We did not locate any studies of other potentially effective nonsurgical modalities (relaxation, yoga, cognitive-behavioral therapy, etc.).

The quality of those studies providing data about the prevalence of comorbidities varied by comorbidity, with the bulk of studies assessed as poor quality for a given condition (Appendix E). Among studies reporting data on the prevalence of comorbidities, the range of prevalence estimates tended to be more narrow in those studies that employed validated diagnostic criteria (e.g., Rome criteria for irritable bowel syndrome [IBS]), and studies using validated criteria were of higher quality.

Few intervention studies were rated as good[68, 83] or fair[49, 72, 85]quality. The higher quality evidence tended to demonstrate a lack of benefit: lysis of adhesions showed no benefit,[83] a selective estrogen receptor modulator (SERM) had a negative effect on pain and the trial was stopped early.[68, 76] Some higher quality studies also suggested benefit of some approaches including depot leuprolide for endometriosis-associated CPP[72] and botulinum toxin for myofascial-related CPP.[85]

The literature overall is muddled by a lack of standardized definitions for CPP and unclear diagnostic evaluation that make it difficult to determine whether studies are truly including women with CPP. Systematic reviews of effectiveness of interventions for a symptom or syndrome are fraught with difficulty; the lack of specific diagnostic criteria results in heterogeneity within and across studies. In order to effectively treat any chronic pain, one would assume that a thorough diagnostic investigation would first take place. For many conditions, this typically follows some pre-determined algorithm. However, for CPP, no such algorithm exists. Thus, in each study (and likely for each private practitioner), the patient is approached in a variable manner, and some possible diagnoses may or may not be ruled out before treatment begins. There is no assurance that the treated condition is the causative condition. Treating a symptom means that a study group will likely have a variety of etiologies – some may be amenable to the intervention under study, others may not. Compared to an intervention trial that follows established diagnostic criteria and targets an identified condition, dilution of potential benefits and harms may be occurring.

Summary of Outcomes by Key Question

KQ1. Prevalence of comorbidities. We located 24 articles [10, 13-15, 62-80, 82] comprising 21 unique study populations addressing the prevalence of our comorbidities of interest. The prevalence rates for the co-morbidities we examined showed significant variation. Frequently no operational definition or diagnostic criteria were provided. When definitions or criteria were available, they were rarely consistent across studies. Methods of making diagnoses varied and included patient report of symptoms, patient report that they were given the diagnosis by a health care provider, evaluation by a health care provider, and objective diagnostic criteria. Undoubtedly these inconsistencies in defining the co-morbidities and making the diagnoses contributed to the variation.

KQ2. Effectiveness of surgical approaches. Seven unique studies addressed surgical interventions for CPP in women.[49, 52, 62, 66, 71, 83, 84] Given that many women with CPP are treated with invasive surgical procedures, remarkably little evidence exists that supports a surgical approach to the treatment of CPP. We identified and reviewed 2 studies comparing non-specific surgical approach to nonsurgical approach for CPP therapy,[62, 66] one study addressing hysterectomy specifically,[52] one study evaluating laparoscopic adhesiolysis at the time of diagnostic laparoscopy,[83] 2 studies evaluating laparoscopic utero-sacral nerve ablation (LUNA) comparing to diagnostic laparoscopy,[49, 71] and one paper directly comparing LUNA and utero-sacral ligament resection.[84]

In none of the studies with comparison data was surgery in general or any specific surgical technique better than either nonsurgical intervention or the comparator technique in improving pain status in patients. Given the limited number of studies addressing heterogeneous surgical interventions and so few of good or fair quality, it is impossible to summarize the evidence for the effect for surgical interventions on any of the outcomes proposed. The most common surgical technique used as control in comparison trials was diagnostic laparoscopy; however, the direct therapeutic benefit of this procedure is poorly understood, and its role as a stand-alone surgical intervention for the treatment of CPP remains to be determined. The evidence is insufficient to conclude that surgical intervention is either effective or ineffective for the treatment of CPP.

KQ3. Evidence for differences in treatment outcomes by etiology. We did not locate studies addressing whether surgical outcomes differ if an etiology for CPP is identified after surgery.

KQ4. Effectiveness of nonsurgical approaches. We located 17 articles[52, 62, 63, 66, 68, 72-74, 76, 85-92] comprising 16 unique studies addressing nonsurgical approaches for CPP. Overall, little good quality data was available. This was usually due to a lack of reporting or significant bias, either for lack of blinding or failure to analyze by intent-to-treat.

Within our included studies, there was significant variation in study design that did not allow us to synthesize results or perform a meta-analysis. This significantly detracts from the ability to apply these study results to a broader population or provide concrete estimates for clinical effect. We saw this variation in definition of pelvic pain, patient populations, outcome measures, interventions, timing of outcome measures and participant follow-up, and comparators.

Only 3 of the 16 studies utilized a placebo arm for comparison. All of the other studies employed active treatments as comparators. As noted earlier, this lack of placebo comparison detracts from the active head-to-head trials because no initial validation of effect has been made.

It could easily be assumed that each active intervention works simply by placebo effect, and this could explain why each hormone-based treatment seems equally effective in our review.

Eight of 16 studies evaluated hormone-based therapies for the treatment of pelvic pain. This is likely a result of most participant populations being recruited from endometriosis-based pain centers. However, it is well known that endometriosis is only one of many etiologies for pelvic pain, and hormone therapies one of many pain treatments.

The majority of the available literature focuses on hormone-based medical treatments, thus indirectly assuming that the majority of pelvic pain is gynecologic and/or endometriosis-driven. This bias toward gynecologic-based pain diagnoses is reflected in the absence of a true diagnostic work-up in most of these studies.

KQ5: Evidence for choosing intervention approaches. We did not identify any comparative studies of interventions for CPP in participants who had a prior intervention that failed to achieve the target outcome(s).

Strength of the Evidence for Effectiveness of Therapies

Overview

We assessed the literature by considering both the observed effectiveness of interventions and the confidence that we have in the stability of those effects in the face of future research. The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence and can be insufficient, low, moderate or high. Strength of evidence describes the adequacy of the current research, both quantity and quality, and whether the entire body of current research provides a consistent and precise estimate of effect. Interventions that have shown significant benefit in a small number of studies but have not yet been replicated using rigorous study designs will have insufficient or low strength of evidence, despite potentially offering clinically important benefits. Future research may find that the intervention is either effective or ineffective.

Methods for applying strength of evidence assessments are established in the Evidence-based Practice Centers' (EPCs) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[61] and are based on consideration of 4 domains: risk of bias, consistency in direction of the effect, directness in measuring intended outcomes, and precision of effect. We determined the strength of evidence for effectiveness outcomes (KQ 2-5) and assessed the body of literature deriving from studies that included comparison groups.

Tables 15 and 17 provide summaries of results, including strength of evidence, for each category of intervention addressing each key question. Tables 16 and 18 document the strength of evidence for each domain of the major intervention-outcome combinations.

Strength of the Evidence by Key Question

KQ1. Prevalence of comorbidities. We did not assess the strength of evidence for studies addressing this key question as we were interested in data regarding the prevalence of comorbid conditions and not effectiveness of interventions.

KQ2. Effectiveness of surgical approaches. We rated the strength of evidence for the effect of surgery on improving pain status as low or insufficient overall. The strength of evidence was insufficient specifically for the comparison between a general surgical approach to CPP

treatment as compared to nonsurgical approach. There were 2 studies in this area, one poor quality RCT[66] and one poor quality prospective cohort,[62] which were at high risk of bias, but did demonstrate consistent estimates of effects. With 2 RCTs, one of fair[49] and one of poor quality,[71] we considered the strength of evidence to be low for the lack of efficacy of LUNA to improve pain status over diagnostic laparoscopy alone. Both studies were consistent in the findings, with direct comparisons and precise measures, but were also subjected to potentially high levels of bias. The evidence was insufficient due lack of comparison studies to measure the effect of hysterectomy and utero-sacral ligament resection on improvement of pain status. The strength of evidence for the effect of adhesiolysis on pain status was insufficient based on one good quality RCT.[66]

The evidence was insufficient to evaluate the effects of surgical treatment on any of the other prescribed outcome measures, i.e., improving functional status, satisfaction with care or quality of life, because lack of comparison studies, multiple studies and studies with significant risk of bias.

Table 15. Summary of results and strength of evidence of studies assessing surgical interventions

Intervention	Study design/Quality	Study results and overall strength of evidence
Surgical vs. nonsurgical therapy	1 RCT / 1 poor[66] 1 prospective cohort / 1 poor[62]	• Equivalent improvements for both surgical and nonsurgical therapy in pain status • Nonsurgical therapy with an integrated treatment approach without routine diagnostic laparoscopy improved functional status over surgical therapy with routine diagnostic laparoscopy in 1 study • Strength of evidence for lack of difference in improving pain status is insufficient • Strength of evidence for improving functional status is insufficient with only one RCT of poor quality
Hysterectomy vs. nonsurgical therapy	1 prospective cohort / 1 poor[52]	• Improvement in pain status for both groups, but no group comparison • Strength of evidence for improving pain status is insufficient with 1 prospective cohort of poor quality
Laparoscopic adhesiolysis vs. diagnostic laparoscopy	1 RCT / 1 good[83]	• No significant difference on improvement of pain status • No significant difference between the groups in quality of life scores • Strength of evidence for lack of difference in improving pain status is insufficient, with 1 RCT of good quality • Strength of evidence for improving quality of life is insufficient with 1 RCT of good quality

Table 15. Summary of results and strength of evidence of studies assessing surgical interventions (continued)

Intervention	Study design/Quality	Study results and overall strength of evidence
LUNA vs. diagnostic laparoscopy	2 RCT / 1 fair,[49] 1 poor[71]	• No significant difference on improvement in pain status • No difference on improvement in quality of life between groups in one study • Strength of evidence for lack of difference in improving pain status is low • Strength of evidence for improving quality of life is insufficient with 1 RCT of poor quality
LUNA vs. utero-sacral ligament resection	1 RCT / 1 poor[84]	• No significant difference on improvement of pain status • Strength of evidence of improving pain status is insufficient with 1 RCT of poor quality

LUNA=laparoscopic utero-sacral nerve ablation; RCT=randomized controlled trial;

Table 16 summarizes assessments in each domain comprising strength of evidence for studies of surgical approaches.

Table 16. Strength of evidence domains for studies assessing surgical approaches to CPP

Study	No. of Studies (N participants)	Risk of Bias	Consistency	Directness	Precision	SOE	Magnitude of Effect
Pain Status: Reduction in Pain							
Surgery vs. nonsurgical therapy							
Peters et al.[66], Lamvu et al.[62]	2 (476)	High	Consistent	Direct	Imprecise	Insufficient	No difference between treatment groups
Hysterectomy vs. nonsurgical therapy							
Carlson et al.[52]	1 (118)	High	Unknown	Direct	Precise	Insufficient	Improvement in both treatment groups; no comparison
Laparoscopic adhesiolysis vs. diagnostic laparoscopy							
Swank et al.[83]	1 (98)	Low	Unknown	Direct	Imprecise	Insufficient	No statistically significant intergroup difference in pain scale measures
LUNA vs. diagnostic laparoscopy							
Daniels et al.[49], Johnson et al.[71]	2 (466)	High	Consistent	Direct	Precise	Low	No difference between treatment groups

Table 16. Strength of evidence domains for studies assessing surgical approaches to CPP (continued)

Study	No. of Studies (N participants)	Risk of Bias	Consistency	Directness	Precision	SOE	Magnitude of Effect
Pain Status: Reduction in Pain							
LUNA vs. utero-sacral ligament resection							
Palomba et al.[84]	1 (74)	High	Unknown	Direct	Imprecise	Insufficient	No difference between treatment groups
Pain Status: Activities of Daily Living							
Surgery vs. nonsurgical therapy							
Peters et al.[66]	1 (106)	High	Unknown	Direct	Imprecise	Insufficient	Improvement in ADL: Integrated 39/57; Standard 18/49
Functional Status							
Surgery vs. nonsurgical therapy							
Peters et al.[66]	1 (106)	High	Unknown	Direct	Precise	Insufficient	Improved in integrated, nonsurgical group vs. surgical group
Patient Satisfaction with Pain Management							
Hysterectomy vs. nonsurgical therapy							
Carlson et al.[52]	1 (146)	High	Unknown	Direct	Imprecise	Insufficient:	Hysterectomy 68/75; Nonsurgical 50/71
Quality of Life							
Laparoscopic lysis of adhesions compared to laparoscopic surgery without adhesiolysis							
Swank et al.[83]	1 (98)	Low	Unknown	Direct	Imprecise	Insufficient	No statistically significant intergroup difference in pain scale measures

ADL=activities of daily living; LUNA=laparoscopic utero-sacral nerve ablation; N=number; SOE=strength of evidence

KQ3. Evidence for differences in treatment outcomes by etiology. We did not locate studies addressing whether surgical outcomes differ if an etiology for CPP is identified after surgery.

KQ4. Effectiveness of nonsurgical approaches. We found few studies addressing nonsurgical therapies. In 2 of the 5 categories (antineuropathic agents and neuromuscular blocking agents), we found only one study, so evidence in this area is insufficient to evaluate effects on outcomes assessed as there are no comparison studies. Among hormonal therapies and nonpharmacologic interventions, none of the 10 studies used the same intervention or comparator (Table 17), thus we have insufficient evidence to evaluate effects for outcomes in these as well.

For the primary outcomes, the interventions were evaluated to have insufficient strength of evidence, often because of single study. Studies generally had high risk of bias and frequent imprecision, often because studies were either too diverse in interventions and outcomes studied to summarize, or because the field is early in its development (Table 18.).

Table 17. Summary of results and strength of evidence for studies assessing nonsurgical treatments for CPP

Intervention	Study design/ Quality	Study results and overall strength of evidence
Hormonal therapies	7 RCTs / 1 good,[68, 76] 1 fair,[72] 5 poor[73, 74, 88-90] 1 nRCT / 1 poor[87]	• Multiple interventions between studies, most without a placebo as comparator • Many were not blinded to participant • Overall, most hormone therapies show clinically significant improvement in pain, but unable to rate one as superior to another • Insufficient evidence to determine effectiveness
Antineuropathic agents	1 RCT/ 1 poor[63]	• All 3 arms experience clinically significant reduction in pain • Insufficient evidence to determine effectiveness
Neuromuscular blocking agents	1 RCT / 1 fair[85]	• Clinically significant reduction in pain with intervention group compared to placebo • Insufficient evidence to determine effectiveness
Nonpharmacologic therapies	4 RCTs / 1 fair[93], 3 poor[66, 91, 92]	• Integrated treatment approach, pelvic ultrasonography plus counseling, and pelvic floor muscle therapy showed clinically significant reduction in pain • Photographic-enhanced post-operative counseling showed no benefit • Insufficient evidence to determine effectiveness
Surgical vs. Nonsurgical approaches	2 prospective cohort studies/ 2 poor[52, 62]	• Equivalent improvements for both varied surgical and nonsurgical therapy in pain status • Improvement in pain status for individuals electing hysterectomy vs. nonsurgical management, but no group comparison • Strength of evidence is insufficient with 2 poor quality cohort studies

CPP=noncyclic chronic pelvic pain; nRCT=non-randomized controlled trial; RCT=randomized controlled trial

Table 18 summarizes domain scores for each of the domains comprising strength of effectiveness (risk of bias, consistency, directness, and precision).

Table 18. Strength of evidence domains for studies assessing nonsurgical approaches to CPP

Study	Number of studies (N participants)	**Domains pertaining to Strength of Evidence (SOE):**				**SOE**
		Risk of Bias	Consistency	Directness	Precision	Overall SOE and Magnitude of Effect
Pain Status: Time to return of pain						
Raloxifene vs. Placebo						
Stratton et al.[68, 76]	1 (93)	Low	Unknown	Direct	Imprecise	Insufficient: quicker return to pain with Raloxifene (OR 2.81, 95%CI 1.41–6.19)
Pain Status: Reduction in Pain						
GnRH analogue vs. GnRH analogue + E2/norethindrone vs. Estroprogestin						
Zupi et al.[88]	1 (133)	High	Unknown	Direct	Precise	Insufficient: improvement in both treatment groups, greater in GnRH (52% vs. 6%)
Depo leuprolide vs. Placebo						
Ling et al.[72]	1 (86)	Medium	Unknown	Direct	Precise	Low: greater reduction in pain with treatment (81% vs. 36%)
Gestrinone vs. Depo leuprolide						
Gestrinone Study Group[74]	1 (55)	High	Unknown	Direct	Imprecise	Insufficient: no statistically significant intergroup differences.
Goserelin vs. Monophasic OCP + E2						
Vercellini et al.[73]	1 (57)	High	Unknown	Direct	Imprecise	Insufficient: no statistically significant intergroup differences.
Estroprogestin vs. GnRH agonist + estroprogestin						
Parazzini et al.[90]	1 (97)	High	Unknown	Direct	Imprecise	Insufficient: no statistically significant intergroup differences.
Botulinum toxin vs. Placebo						
Abbott et al.[85]	1 (60)	Medium	Unknown	Direct	Imprecise	Insufficient: no statistically significant intergroup differences.
Gabapentin vs. Amitryptyline vs. Gabapentin + Amitryptyline						
Sator-Katzenschlager et al.[63]	1 (56)	High	Unknown	Direct	Imprecise	Insufficient: groups with gabapentin showed greater improvement at 12mo: pain score 1.5/10 ± 0.9 vs. 2.2/10 ± 1.6
Distention of pelvic floor muscles vs. Counseling						
Heyward et al.[86]	1 (50)	High	Unknown	Direct	Imprecise	Insufficient: Improvement in treatment group VAS (35/100 vs. 0/100)
Photographic post-operative counseling vs. without photos						
Onwude et al.[91]	1 (233)	High	Unknown	Indirect	Imprecise	Insufficient: no difference in groups

Table 18. Strength of evidence domains for studies assessing nonsurgical approaches to CPP (continued)

Study	Number of studies (N participants)	**Domains pertaining to Strength of Evidence (SOE):**	**SOE**	Study	Number of studies (N participants)	**Domains pertaining to Strength of Evidence (SOE):**
Pain Status: Reduction in Pain						
Standard treatment for pelvic pain vs. integrated approach						
Peters et al.[66]	1 (112)	High	Unknown	Direct	Imprecise	Insufficient: No difference in McGill Pain Score
Pelvic ultrasonography vs. expectant management						
Ghaly [92]	1 (100)	High	Unknown	Direct	Imprecise	Insufficient: Greater reduction of pain with intervention (26% vs. 9%)
Hysterectomy vs. nonsurgical therapy						
Carlson et al.[52]	1 (118)	High	Unknown	Direct	Precise	Insufficient: Improvement in both treatment groups; no comparison
Surgical vs. nonsurgical therapy						
Lamvu et al.[62]	1 (370)	High	Consistent	Direct	Imprecise	Insufficient No difference between treatment groups
Pain Status: Activities of Daily Living						
Standard treatment for pelvic pain vs. integrated approach						
Peters et al.[66]	1 (112)	High	Unknown	Direct	Imprecise	Insufficient: Improvement in ADL: Integrated 39/57; Standard 18/49
Patient Satisfaction with Treatment						
Depo medroxy-progesterone vs. Monophasic OCPs + Danazol						
Vercellini et al.[89]	1 (80)	High	Unknown	Direct	Precise	Insufficient: no statistically significant intergroup differences.
Vaginal ring vs. Transdermal patch						
Vercellini et al.[87]	1 (207)	High	Unknown	Direct	Imprecise	Insufficient: More satisfied with ring (RR, 1.50; 95% CI, 1.17–1.93), pain reduced in both groups
Hysterectomy vs. nonsurgical therapy						
Carlson et al.[52]	1 (146)	High	Unknown	Direct	Imprecise	Insufficient: Hysterectomy 68/75; Nonsurgical 50/71

ADL=activities of daily living; CPP=noncyclic chronic pelvic pain; E2=estradiol; GnRH=gonadotropin releasing hormone; OCP=oral contraceptive pill; OR=odds ratio; RR=relative risk; SOE=strength of evidence; VAS=visual analog scale

KQ5: Evidence for choosing intervention approaches. We did not identify any comparative studies of interventions for CPP in participants who had a prior intervention that failed to achieve the target outcome(s).

Applicability

We set inclusion criteria intended to identify studies with applicability to women with noncyclic or mixed CPP. Studies differed considerably in terms of study populations, interventions, and outcome measures (Table 19). Many of the studies were noncomparative.

Table 19. Summary of outcome measures

Study, year	0-10 point VAS	0-100 point VAS	10 cm VAS	100 mm VAS	140 mm VAS	Activity Index	Andersch and Milson Verbal Pain Scale	Biberoglu and Behrman scale	Beck Depression Inventory	EQ-VAS	EuroQOL EQ-5D	General and Mental Health Indices	McGill Pain Questionnaire	Medication Quantification Scale	MOS SF 12 or 36	Pain diary	Pain interview	Sexual Activity Questionnaire	Social Readjustment Rating Scale	Symptoms interview	Verbal Pain Rating Scale	Other pain or symptoms duration scale	Other QOL scale	Other pain rating scale
RCTs																								
Daniels et al., 2009[49]			✓							✓	✓													
Stratton et al., 2008[68]	✓																							✓
Palomba et al., 2006[84]	✓			✓																				
Heyman et al., 2006[86]		✓																				✓		
Abbott et al., 2006[85]		✓									✓				✓			✓						
Sator-Katzen-schlager et al., 2005[63]	✓																							

Table 19. Summary of outcome measures (continued)

Study, year	0-10 point VAS	0-100 point VAS	10 cm VAS	100 mm VAS	140 mm VAS	Activity Index	Andersch and Milson Verbal Pain Scale	Biberoglu and Behrman scale	Beck Depression Inventory	EQ-VAS	EuroQOL EQ-5D	General and Mental Health Indices	McGill Pain Questionnaire	Medication Quantification Scale	MOS SF 12 or 36	Pain diary	Pain interview	Sexual Activity Questionnaire	Social Readjustment Rating Scale	Symptoms interview	Verbal Pain Rating Scale	Other pain or symptoms duration scale	Other QOL scale	Other pain rating scale
RCTs																								
Johnson et al., 2004[71]	✓																							
Onwude et al., 2004[91]					✓								✓				✓							
Zupi et al., 2004[88]	✓														✓									
Swank et al., 2003[83]		✓												✓	✓						✓			
Ling at al., 1999[72]	✓							✓					✓			✓								
Gestri-none Study Group, 1996[74]			✓					✓																
Vercellini et al., 1996[89]	✓							✓																
Ghaly, 1994[92]													✓											
Vercellini et al., 1993[73]	✓						✓	✓																
Peters et al., 1991[66]													✓			✓				✓				

Table 19. Summary of outcome measures (continued)

Study, year	0-10 point VAS	0-100 point VAS	10 cm VAS	100 mm VAS	140 mm VAS	Activity Index	Andersch and Milson Verbal Pain Scale	Biberoglu and Behrman scale	Beck Depression Inventory	EQ-VAS	EuroQOL EQ-5D	General and Mental Health Indices	McGill Pain Questionnaire	Medication Quantification Scale	MOS SF 12 or 36	Pain diary	Pain interview	Sexual Activity Questionnaire	Social Readjustment Rating Scale	Symptoms interview	Verbal Pain Rating Scale	Other pain or symptoms duration scale	Other QOL scale	Other pain rating scale
nRCTs																								
Vercellini et al., 2010[87]				✓				✓																
Prospective cohort studies																								
Lamvu et al., 2006[62]									✓				✓											
Carlson et al., 1994[52]						✓						✓								✓			✓	✓

nRCT=non-randomized controlled trial; QOL=quality of life; RCT=randomized controlled trial; VAS=visual analog scale

Lack of direct comparisons of treatment options further hinders our ability to know what findings will best extend to a specific patient or to decisions about care protocols within clinics or health systems. Overall the data that are available have fair to good applicability to women with noncyclic/mixed CPP populations in settings within the United States. Table 20 summarizes applicability of the evidence across the studies included in this review; Appendix F contains applicability tables for individual key questions.

Table 20. Applicability of the noncyclic CPP evidence

Domain	Description of applicability of evidence
Population	The study populations represented by the reviewed studies consist of either highly selected women with CPP presenting to high-level referral centers specializing in CPP care or broader groups of women recruited from general gynecologic practices without CPP specialization. The patients referred to or attracted to this type of care are often different than the types of patients who present to a primary care physician or local gynecologist for the treatment of pelvic pain. Some of the findings, may not be generally applicable to larger populations. Specific intervention comparator studies generally were single institution studies, which may not be applicable to general populations. Participants were almost exclusively recruited from academic centers. Considering this, the participants in the included studies may not represent the typical pelvic pain patient—they could easily have a more refractory illness or complicating factors that precipitate referral. Patients in primary care practices and general obstetrics and gynecology practices may experience more improvement with the same treatments than the study populations. A preponderance of studies focused primarily on endometriosis-based CPP; for patients without endometriosis or with milder disease, these studies' findings cannot be applied.
Intervention	Interventions described as integrative care, involving multiple disciplines would be difficult to duplicate outside of specialty centers. Several of the hormonal therapies required complex or multi-disciplinary algorithms and close follow-up. Some of the interventions may not be applicable to general population of women with CPP. Laparoscopic lysis of abdominal adhesions, for example, is only applicable to a subset of women with CPP who undergo diagnostic laparoscopy and have visible adhesions.
Comparators	Most of the studies compared one treatment paradigm to another, which is appropriate to clinical practice. The lack of placebo-controlled trails in the studies, while detrimental to overall study strength, improves applicability.
Outcomes	Only 2 studies reported reduction of pain by 30% or 50%, which are the outcome measures deemed to be of clinical significance in the pain literature. Many patients are limited in activities of daily living or quality of life; reports of these outcomes are applicable to most of the patients with noncyclic CPP. Few studies assessed outcome variables such as functional status, quality of life or satisfaction with care. The outcomes measured mostly included a form of the VAS. While helpful to measure improvement in pain ratings, most patients clinically desire not only improvement in pain, but in day-to-day functionality and quality-of-life. Similarly, few studies looked at overall treatment satisfaction which, in practice, typically drives the selection of certain treatments over others.
Setting	The settings in which studies were conducted was highly diverse, which limits general applicability of any findings. When specified, all surgical procedures were performed at facilities with operating rooms, but the various levels of specialty and referral care were quite disparate. Most of the studies were set in large academic centers; many of these were European.

CPP=noncyclic chronic pelvic pain; VAS=visual analog scale

Applicability of the Evidence for Surgical Approaches

The study populations represented by the reviewed studies consist of either highly selected women with CPP presenting to high-level referral centers specializing in CPP care or broader groups of women recruited from general gynecologic practices without CPP specialization. Some of the findings, therefore, may be generally applicable to larger populations, while some may not

be applicable. Specific intervention comparator studies generally were single institution studies, which may not be applicable to general populations.

Several interventions are represented in the reviewed studies, some of which may not be applicable to general population of women with CPP. Laparoscopic lysis of abdominal adhesions, for example, is only applicable to a subset of women with CPP who undergo diagnostic laparoscopy and have visible adhesions.

Most studies compared surgical (non-specific) interventions to nonsurgical interventions or specific surgical techniques to diagnostic laparoscopy alone. One study compared 2 active interventions, LUNA to utero-sacral ligament resection. The outcomes assessed by the various studies were not uniform. All studies measured the effect of interventions of pain status, but the measurement techniques and definitions for improvement or comparison were generally not uniform. Few studies assessed other outcome variables, such as functional status, quality of life or satisfaction with care.

The settings in which studies were conducted was highly diverse, which limits general applicability of any findings. When specified, all surgical procedures were performed at facilities with operating rooms, but the various levels of specialty and referral care were quite disparate.

Applicability of the Evidence for Nonsurgical Approaches

Within studies addressing surgical approaches, participants were recruited from academic centers (16/16) and of those, 11/16 were European and one was conducted in Australia. The patients referred to or attracted to this type of care may be different than the types of patients who present to a primary care physician or local gynecologist for the treatment of pelvic pain. Considering this, the participants in the included studies may not represent the typical pelvic pain patient—they could easily have a more refractory illness or complicating factors that precipitate referral. Patients in primary care practices and general obstetrics and gynecology practices may experience more improvement with the same treatments than the study populations. Another factor which may contribute to this is the preponderance of endometriosis-based CPP within the included articles. Eight of 16 studies focused primarily on endometriosis-associated pain. Thus, for patients without endometriosis or with milder disease, these studies' findings cannot be applied.

The interventions employed are highly variable. There was a large focus on hormone therapies, which are a common first-line therapy in many gynecology practices. However, because many of these studies took place in Europe, the same drugs may not be available in the United States and other countries. Thus, the results may not directly translate. Also, being located in academic centers, often the intervention is more than just a medication but also includes a significant interaction with the treatment team and multi-disciplinary therapies. For most primary care and gynecology practices, this type of treatment algorithm may be difficult to replicate; thus similar results may not be possible.

These interventions were often compared to other active treatments, which is common in practice. Many patients often switch between therapies when one becomes ineffective or intolerable. The lack of placebos, while detrimental to overall study strength, improves applicability.

The outcomes measured mostly included a form of the visual analogue scale (VAS). While helpful to measure improvement in pain ratings, most patients clinically desire not only improvement in pain, but in day-to-day functionality and quality of life. These were not often

assessed. Similarly, few studies looked at overall treatment satisfaction which, in practice, typically drives the selection of certain treatments over others.

Future Research

Gaps in Areas of Research

Research addressing therapies for CPP is largely composed of trials of active agents or approaches with little placebo-controlled research and little evidence of thorough identification of patient characteristics and potential etiologies for CPP. Notably, we did not locate any studies providing evidence that surgical outcomes differ if the etiology of CPP is identified after surgery (KQ3). We did not locate any studies providing evidence for choosing one intervention over another to treat persistent or recurrent CPP after an initial intervention failed to achieve the target outcome(s) (KQ5).

The following sections outline gaps in the literature and future research needs.

Etiology. The causes of CPP are not well understood and may be associated with gynecologic (e.g. endometriosis) and nongynecologic (e.g., irritable bowel syndrome [IBS]) conditions. Diagnosis of an underlying cause is complicated because the pain is rarely associated with a single underlying disorder or contributing factor. Future research needs include:

- Analysis of distribution of the underlying causes of CPP
- Longitudinal studies to identify subgroups at risk of developing CPP. Once these populations are identified, preventive strategies can then be investigated.
- Developing understanding of the role of pelvic floor myofascial dysfunction in CPP
- Developing understanding of the role of visceral hyperalgesia in CPP
- Assessment of the effects of variations in sex steroid hormone levels on pain perception in both pain-free women and those with CPP.

Iatrogenic pain. Iatrogenic pain (pain resulting from a procedure or complication of a procedure performed by a clinician) is another understudied etiologic factor for CPP. Emerging causes of iatrogenic pain include use of permanent mesh (post-mesh pain syndrome), tubal ligation/occlusion (post-tubal syndrome), and endometrial ablation (post-ablative pain syndrome). Because these women are often not followed for long periods of time and no formal reporting system for complications exists, the prevalence of chronic pain in these women is likely underappreciated.

It is imperative that, in addition to studying chronic pain that emerges de novo, practitioners look inward at how the medical community may be contributing to the chronic pelvic pain problem. Prevention of iatrogenic pain may be the key to saving many CPP patients from years of treatment and decreased quality of life. Future research needs related to iatrogenic causes of CPP include:

- Understanding benefits and harms of interventions for newer procedures to treat pelvic organ prolapse and uterine bleeding
- Assessing chronic post-operative incisional pain as factor contributing to CPP
- Understanding the role of repeat surgeries in the same location with declining benefit as a pain source
- Raising awareness of the importance of identifying an etiology for pain prior to hysterectomy with or without castration in young women.

Impact and resource utilization. CPP accounts for an estimated 1 in 10 outpatient gynecology visits, and an estimated $1.2 billion per year is spent on outpatient management of CPP in the United States (adjusted for inflation from $880M in 1996).[10] To understand better how to manage CPP care, future research needs include:

- Assessment of the impact of CPP on the use of health services
- Economic analysis to determine most cost effective diagnosis and management strategies.

Standardized definitions and diagnostic criteria. As noted in this review and previous studies,[94] definitions of CPP vary across the literature and may conflate noncyclic and cyclic pain; table 21 outlines definitions of CPP used in the studies comprising this review. Employing standardized definitions of CPP is a critical need in future research to establish clearly the condition under study and the effects of specific therapies. The lack of a standardized conception of CPP likely leads to a dilution of treatment effects that may be present, and clarifying our understanding of patient populations can help to bring treatment outcomes into focus. Similarly, few studies reporting comorbidity data used validated tools to diagnose comorbidities, and may relied on patient self-report. Future research needs related to defining and diagnosing CPP and comorbid conditions include:

- Widespread use of accepted definitions of CPP across studies
- Standard use of validated tools in studies to inform our understanding of the true prevalence of conditions reported to co-occur with CPP.
- Larger, prospective studies examining the extent to which comorbidities modify treatment approaches and outcomes in CPP.

Table 21. Descriptions/definitions of CPP in studies assessed

Study	CPP description/definition
Vercellini et al., 2010[87]	Persistent pelvic pain (dysmenorrhea, dyspareunia, nonmenstrual pelvic pain) of more than 6 months' duration
Daniels et al., 2009[49]	Noncyclical pain, dysmenorrhea, or dyspareunia lasting longer than 6 months, located within and below the anterior iliac crests
Montenegro et al., 2009[69]	Continuous or recurrent pain in the lower abdomen or pelvis lasting at least 6 months, not related to pregnancy, and sufficiently severe to interfere with habitual activities; CPP excludes pain occurring exclusively in association with menstruation or during sexual intercourse
Pitts et al., 2008[70]	Any type of pain in the pelvic region including dysmenorrhea, dyspareunia, and pelvic pain not occurring with periods of intercourse, either on and off or constantly
Stratton et al., 2008[68, 76]	Pelvic pain for at least 3 months
Fenton et al., 2007[77]	NR
Paulson et al., 2007[78]	Constant or intermittent pain of greater than 6-month duration is present in the pelvic area and lower abdomen
Abbott et al., 2006[85]	Chronic pelvic pain (dysmenorrhea, dyspareunia, dyschezia, and nonmenstrual pelvic pain) causing disruption to daily activities
Grace et al., 2006[14, 15]	Pain in the lower abdomen of at least 6 months duration that is not associated with menstruation or sexual activity

Table 21. Descriptions/definitions of CPP in studies assessed (continued)

Study	CPP description/definition
Heyman et al., 2006[86]	Acyclic pain of at least 6-months duration; pain is typically dull, with diffuse aching throughout the lower abdomen or localized at the iliac fossa. Pain may increase pre- and paramenstrually. Upon rectal palpation, the findings in CPP consist of tenderness of the following structures: the musculature of the pelvic floor and possibly the coccygeal vertebrae and/ or the sacrotuberous/spinal ligaments
Lamvu et al., 2006[62]	Noncyclic pain of at least 6 months duration, localized to the pelvis, anterior abdominal wall, at or below the umbilicus and lower back and buttocks
Verit et al., 2006[82]	Pain longer than 6 month's duration, not exclusively associated with menstrual periods or sexual intercourse
Tu et al., 2006[79]	NR
Palomba et al., 2006[84]	Severe midline pelvic pain persisting for more than 6 months and unresponsive to common medical treatment
Sator-Katzenschlager et al., 2005[63]	Chronic pelvic pain persisting longer than 6 months
Williams et al., 2005[64, 67]	Extended duration of pain in the pelvis; pain may originate from any organ system or pathology and may have multiple contributing factors
Zupi et al., 2004[88]	NR
Johnson et al., 2004[71]	Pelvic pain present as dysmenorrhea (primary or secondary), nonmenstrual pain, deep dyspareunia (pain with sexual intercourse) or dyschezia (defecatory pain) from more than 6 months
Onwude et al., 2004[91]	NR
Chung et al., 2003[65]	Noncyclic abdominal and pelvic pain lasting at least 6 months
Swank et al., 2003[83]	Continuous or intermittent abdominal pain of at least 6 months' duration
Zondervan et al., 2001[13]	Constant or intermittent pelvic pain of ≥6 months' duration, not exclusively associated with menstrual periods or sexual intercourse
Parazinni et al., 2000[90]	Pelvic pain lasting 3–12 months after laparoscopy or laparotomy
Bodden-Heidrich et al., 1999[80]	Chronic pain in the lower abdomen lasting longer than 6 months
Ling et al., 1999[72]	Chronic pelvic pain for at least 6 months unrelated to menstruation
Gestrinone Italian Study Group, 1996[74]	NR
Matthias et al., 1996[10]	Pain below the belly button or in the female organs for at least 6 months
Saravelos et al., 1995[75]	Pain in the pelvis persisting for ≥ 6 months
Carlson et al., 1994[52]	Pain of at least 6 months duration
Ghaly, 1994[92]	Pain of at least 6 months duration
Vercellini et al., 1993[73]	NR
Peters et al., 1991[66]	Chronic pelvic pain for at least 3 months
Vercellini et al., 1996[89]	NR

Diagnostic approaches. Standardized, thorough diagnostic approaches are an important area for future study as the literature currently lacks clear delineation of patient populations. Moreover, standardized evaluations can be help to ensure that clinicians are treating the actual cause(s) of CPP versus pain symptoms. The International Pelvic Pain Society has published a clinical assessment document which could be utilized to standardize the initial evaluation of potential participants.[46] Research needs in this area include:

- Estimation of the accuracy of individual and combinations of diagnostic tests for CPP
- Assessing the role of magnetic resonance imaging (MRI) and positron emission tomography (PET)-scan in narrowing the differential diagnosis of CPP
- Development and validation of a new pain assessment tool to capture the multidimensional experience of pelvic pain.

Standardized outcome measures. Studies used numerous outcomes measures to assess pain, quality of life, and patient satisfaction. While studies typically used a VAS measure for pain, VAS scales varied widely (Table 19), making comparisons across studies difficult. Similarly, quality of life measures varied, and patient satisfaction was typically reported using unvalidated instruments. Future research needs should address:

- Use of standardized outcome measures such as those recommended by the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) consensus conference.[95]

Nonsurgical and nonpharmacologic management. The research meeting our criteria largely assessed surgical and pharmacologic, especially hormonal, management of CPP, despite research suggesting the need to consider psychological and sociodemographic factors in understanding and treating chronic pain.[96-100] The few studies to address nonsurgical or nonpharmacologic approaches were generally of poor quality but reported some benefit from a pelvic physiotherapy technique,[86] ultrasonography plus counseling,[92] and an integrated treatment approach[66] emphasizing psychological, dietary, environmental, and physiotherapeutic treatment factors. One study reported no benefit of photographic display of pelvic findings at laparoscopy.[91] Given the importance of a holistic approach to CPP, a better understanding of the potential effects of allied health, integrative medicine, and psychological and behavioral approaches is imperative, and research needs include:

- Studies of nonpharmacologic/nonsurgical interventions for CPP, including: acupuncture, transcutaneous electrical nerve stimulation (TENS), physiotherapy, cognitive behavioral therapy, advice and communication about pain, and education
- Studies of health care settings and consultation styles and their effects on the impact of the treatments for CPP
- High quality assessments of multidimensional treatment packages, including psychological therapies.

Pharmacologic approaches. Much of the literature addressing pharmacologic interventions for CPP investigated hormonal therapies in women with endometriosis-associated CPP, and few studies were placebo controlled. Future research needs include:

- Studies of nonhormonal agents such as tanezumab (a monoclonal antibody against nerve growth factor)
- Placebo-controlled studies.

Surgical compared with nonsurgical approaches. The literature also lacks studies comparing surgical and nonsurgical approaches, and future research in this area is important. Two poor quality cohort studies comparing surgical and nonsurgical approaches reported similar effects on pain status between modalities[52, 62] and greater patient satisfaction with hysterectomy compared with nonsurgical management in one study.[52] One study comparing a standard laparoscopic approach to an integrated approach emphasizing psychological and other treatments reported no differences in pain scores between approaches and improvements in "general pain experience" in the integrated approach arm.[66] Research needs include:

- Prospective, comparative studies addressing commonly employed surgical and medical treatment approaches for CPP.

Benefits of surgical treatment. Another important area for research lies in establishing whether surgical approaches are of benefit for CPP treatment, and if so, which approaches are superior. On study comparing LUNA with diagnostic laparoscopy alone (sham LUNA) reported similar outcomes between approaches.[49, 71] One study reported no benefit of lysis of adhesions compared with laparoscopy alone,[83] and one comparing active approaches (LUNA vs. utero-sacral ligament resection)[84] reported no differences in pain outcomes between groups. Future research needs in this area include:

- Larger, rigorously conducted studies to help determine surgical outcomes, which patients are likely to benefit from surgery, and the optimal timing of intervention
- Research to classify the therapeutic benefit of diagnostic laparoscopy, often used as a standard control arm in surgical studies.

Methodologic Issues

While 17 of the studies identified for this review were RCTs, few adhered to standard study design and reporting conventions as reflected in the generally poor quality of studies. In particular, few trials adequately concealed treatment assignments from participants, investigators, and outcome assessors, and just under half reported an intention-to-treat-analysis (7/17). Eight studies had drop-out rates exceeding 10 percent, and in 6 out of 17 trials, more than 20 percent of participants were lost to followup. Most trials (n=12/17) did report an *a priori* primary outcome of interest and sample size calculation. Ten reported missing or incomplete outcome data adequately.

Among cohort and nonrandomized studies (n=3), none employed blinded outcome assessors, and 1 provided an *a priori* sample size calculation. All studies had significant drop-out rates (> 10 percent). Attention to study design and conduct in future research should aid researchers in drawing conclusions about outcomes of CPP treatment.

As noted, definitions of CPP varied across studies. Among studies reporting definitions for CPP, most (n=23/26) reported a pain duration (typically 6 months), and 5 specified an anatomic location for pain that was more specific than "lower abdomen or pelvis." Five studies included dysmenorrhea or dyspareunia along with noncyclic pain in their definition, and 7 of 33 studies reported no definition for CPP.

Outcome measures similarly varied across studies. While many studies used a VAS scale to assess pain, few studies used the same scale. Quality of life measures used were typically validated tools (e.g., SF 36) but varied among studies. Measures of patient satisfaction were typically not validated. Ideally, future research will better characterize CPP study populations.

Studies were typically of 6 to 12 months duration with few providing long-term followup data after the cessation of an intervention. Future studies should extend the followup period to assess the degree to which outcomes are durable, especially as many women with CPP fail to adequate pain relief despite multiple interventions. RCTs in this literature also typically included fewer than 150 women with CPP, despite the high reported prevalence of CPP. Future research including larger sample sizes should yield greater confidence in treatment effects.

A thorough diagnostic investigation is necessary to treat any chronic pain effectively. For many conditions, this investigation typically follows a pre-determined algorithm, but no such algorithm exists for CPP. Thus, in each study of CPP interventions (and likely for each private practitioner), the patient is approached in a variable manner, and some possible diagnoses may or may not be ruled out before treatment begins. There is no assurance that the treated condition is the causative condition, which certainly influences overall treatment success. We recommend that future studies outline and report the diagnostic process for participants. Pelvic pain researchers would improve the overall quality of literature if an established diagnostic algorithm was developed and put forward for use. A standardized assessment of potential study participants and standardized inclusion criteria would permit systematic analysis of data from multiple trials.

Only 3 trials included here were placebo-controlled; the bulk of nonsurgical studies compared active agents, and no surgical studies used a placebo. A major source of both false positive and false negative results in trials of treatment for pain is the placebo effect, which in analgesic trials is often substantial and may have a duration of weeks or months.[101] The frequency of placebo effects varies among analgesic studies from zero to 100 percent.[101-103] In large double-blind randomized placebo-controlled medication trials, the total percentage of patients receiving placebo reporting a clinically significant effect from the placebo intervention for neuropathic pain or functional pain syndromes is 22 percent.[103] Placebo responses have also been large across a number of clinical trials for treatment of women's sexual dysfunction.[104]

Placebo-controlled trials of any surgical interventions are exceedingly rare. A challenge in interpreting observation trials of surgery, or randomized trials of surgical versus nonsurgical therapy, is that patients could not reasonably be blinded to the intervention,[103] which may be responsible for some overestimation of surgical benefits for pain relief,[105] as surgery can be associated with important placebo effects.[106] Operations that later proved to be useless, including gastric freezing for duodenal ulcers, internal mammary artery ligation for angina pectoris, and knee arthroscopy were initially reported to improve or eliminate the pain of 60 to100 percent of patients for a year after surgery.[101, 107] Based upon the very small number of placebo-controlled randomized trials, the magnitude of the placebo effect of surgery for pain is about 35 percent.[107]

To understand the true effects of therapies for CPP, future research of interventions for relief of CPP should be placebo-controlled, with the exception of small pilot studies to evaluate the potential of a new intervention to be utilized in a future placebo-controlled trial.

Conclusions

The literature addressing therapies for CPP in women is of largely poor quality and inconclusive. While half of the literature comprised RCTs, only 2 were good quality and 3 were fair. Studies providing cross-sectional data about the prevalence of comorbidities varied in quality but were largely poor. Nonetheless, some conclusions can be drawn.

Among studies reporting data on the prevalence of comorbidities, prevalence estimates tended to be more tightly clustered in those studies that employed validated diagnostic criteria (e.g., Rome criteria for IBS), and studies using validated criteria were of higher quality. 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 remain understudied.

Across the literature, higher quality intervention studies tended to demonstrate a lack of benefit: lysis of adhesions showed no benefit,[83] a SERM had a negative effect on pain.[68, 76] Some studies suggest benefit of some approaches including depot leuprolide for endometriosis-associated CPP.[72]

Aside from the lack of benefit reported for adhesiolysis,[83] little evidence demonstrates the effectiveness of surgical approaches. Studies typically reported no differences in improvements in pain scores between groups in studies comparing surgical interventions with diagnostic laparoscopy alone or active surgical interventions. Studies comparing hysterectomy and nonsurgical management[52, 62] reported similar improvements in pain scores between groups and greater patient satisfaction among women undergoing hysterectomy in a sample of women electing hysterectomy.[52]

The strength of evidence for effectiveness across interventions ranges from insufficient to low with few studies comparing the same intervention and variable patient populations. The literature lacks placebo-controlled studies, studies of nonhormonal interventions, studies of nonpharmacologic interventions, and studies comparing medical and surgical management. Studies establishing the benefit of surgery as a treatment option for CPP are also lacking.

Despite a prevalence for CPP rivaling that of widely studied conditions such as asthma,[8] little research assessing therapies exists. While there are many publications regarding pelvic pain, there are relatively few addressing noncyclic CPP, and of those, we evaluated few as providing high quality evidence.

In sum, the literature overall is muddled by a lack of standardized definitions for CPP and unclear diagnostic evaluation that make it difficult to determine whether studies are truly including women with CPP. Similarly, understanding comorbidity prevalence with CPP is difficult as conditions may be considered part of the differential diagnosis or a concomitant condition.

Improved characterization of the targeted condition, intervention, and population in CPP research is necessary to inform treatment choices for this commonly reported entity. A uniform definition of CPP and standardized evaluation of participants are lacking across the literature; study populations likely vary widely, and studies may be reporting effects from treating symptoms rather than a diagnosed condition. Thus our understanding of potential treatment effects is diluted.

References

1. ACOG Practice Bulletin No. 51. Chronic pelvic pain. Obstet Gynecol. 2004 Mar;103(3):589-605.

2. Stones W, Cheong Ying C, Howard Fred M, et al. Interventions for treating chronic pelvic pain in women. Journal [serial on the Internet]. 2005.

3. Leserman J, Zolnoun D, Meltzer-Brody S, et al. Identification of diagnostic subtypes of chronic pelvic pain and how subtypes differ in health status and trauma history. Am J Obstet Gynecol. 2006 Aug;195(2):554-60; discussion 560-1.

4. Howard FM. The role of laparoscopy in chronic pelvic pain: promise and pitfalls. Obstet Gynecol Surv. 1993 Jun;48(6):357-87.

5. Howard FM. Chronic pelvic pain. Obstet Gynecol. 2003 Mar;101(3):594-611.

6. Reiter RC. Evidence-based management of chronic pelvic pain. Clin Obstet Gynecol. 1998 Jun;41(2):422-35.

7. Latthe P, Mignini L, Gray R, et al. Factors predisposing women to chronic pelvic pain: systematic review. BMJ: British Medical Journal. 2006 Apr;332(7544):749-755.

8. Zondervan KT, Yudkin PL, Vessey MP, et al. Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database. Br J Obstet Gynaecol. 1999 Nov;106(11):1149-55.

9. Reiter RC. A profile of women with chronic pelvic pain. Clinical Obstetrics and Gynecology. 1990;33(1):130-136.

10. Mathias SD, Kuppermann M, Liberman RF, et al. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. Obstet Gynecol. 1996 Mar;87(3):321-7.

11. Stanford EJ, Dell JR and Parsons CL. The Emerging Presence of Interstitial Cystitis in Gynecologic Patients with Chronic Pelvic Pain. Urology. 2007;69(4 SUPPL):S53-S59.

12. Zondervan KT, Yudkin PL, Vessey MP, et al. The community prevalence of chronic pelvic pain in women and associated illness behaviour. Br J Gen Pract. 2001 Jul;51(468):541-7.

13. Zondervan KT, Yudkin PL, Vessey MP, et al. Chronic pelvic pain in the community--symptoms, investigations, and diagnoses. Am J Obstet Gynecol. 2001 May;184(6):1149-55.

14. Grace V and Zondervan K. Chronic pelvic pain in women in New Zealand: comparative well-being, comorbidity, and impact on work and other activities. Health Care Women Int. 2006 Aug;27(7):585-99.

15. Grace VM and Zondervan KT. Chronic pelvic pain in New Zealand: prevalence, pain severity, diagnoses and use of the health services. Aust N Z J Public Health. 2004 Aug;28(4):369-75.

16. Steege JF and Stout AL. Resolution of chronic pelvic pain after laparoscopic lysis of adhesions. Am J Obstet Gynecol. 1991 Aug;165(2):278-81; discussion 281-3.

17. Reiter RC and Gambone JC. Nongynecologic somatic pathology in women with chronic pelvic pain and negative laparoscopy. J Reprod Med. 1991 Apr;36(4):253-9.

18. Cheong Y and William Stones R. Chronic pelvic pain: aetiology and therapy. Best Pract Res Clin Obstet Gynaecol. 2006 Oct;20(5):695-711.

19. Clemons JL, Arya LA and Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. Obstet Gynecol. 2002 Aug;100(2):337-41.

20. Hammoud A, Gago LA, Diamond MP, et al. Adhesions in patients with chronic pelvic pain: a role for adhesiolysis? Fertil Steril. 2004 Dec;82(6):1483-91.

21. Jarrell JF, Vilos GA, Allaire C, et al. Consensus guidelines for the management of chronic pelvic pain. J Obstet Gynaecol Can. 2005 Aug;27(8):781-826.

22. Kontoravdis A, Chryssikopoulos A, Hassiakos D, et al. The diagnostic value of laparoscopy in 2365 patients with acute and chronic pelvic pain. Int J Gynaecol Obstet. 1996 Mar;52(3):243-8.

23. Prior A and Whorwell PJ. Gynaecological consultation in patients with the irritable bowel syndrome. Gut. 1989 Jul;30(7):996-8.

24. Stovall TG, Elder RF and Ling FW. Predictors of pelvic adhesions. J Reprod Med. 1989 May;34(5):345-8.

25. Trimbos JB, Trimbos-Kemper GC, Peters AA, et al. Findings in 200 consecutive asymptomatic women, having a laparoscopic sterilization. Arch Gynecol Obstet. 1990;247(3):121-4.

26. van Os-Bossagh P, Pols T, Hop WC, et al. Voiding symptoms in chronic pelvic pain (CPP). Eur J Obstet Gynecol Reprod Biol. 2003 Apr 25;107(2):185-90.

27. Longstreth GF, Preskill DB and Youkeles L. Irritable bowel syndrome in women having diagnostic laparoscopy or hysterectomy. Relation to gynecologic features and outcome. Dig Dis Sci. 1990 Oct;35(10):1285-90.

28. Walker EA, Gelfand AN, Gelfand MD, et al. Chronic pelvic pain and gynecological symptoms in women with irritable bowel syndrome. J Psychosom Obstet Gynaecol. 1996 Mar;17(1):39-46.

29. Riedl A, Schmidtmann M, Stengel A, et al. Somatic comorbidities of irritable bowel syndrome: A systematic analysis. Journal of Psychosomatic Research. 2008 Jun;64(6):573-582.

30. Chung MK. Interstitial cystitis in persistent posthysterectomy chronic pelvic pain. JSLS. 2004 Oct-Dec;8(4):329-33.

31. Treatment of pelvic pain associated with endometriosis. Fertil Steril. 2006 Nov;86(5 Suppl 1):S18-27.

32. Guo SW and Wang Y. The prevalence of endometriosis in women with chronic pelvic pain. Gynecol Obstet Invest. 2006;62(3):121-30.

33. Walker EA, Katon WJ, Hansom J, et al. Psychiatric diagnoses and sexual victimization in women with chronic pelvic pain. Psychosomatics. 1995 Nov-Dec;36(6):531-40.

34. McGowan LPA, Clark-Carter DD and Pitts MK. Chronic pelvic pain: A meta-analytic review. Psychology & Health. 1998 Oct;13(5):937-951.

35. Meltzer-Brody S, Leserman J, Zolnoun D, et al. Trauma and posttraumatic stress disorder in women with chronic pelvic pain. Obstet Gynecol. 2007 Apr;109(4):902-8.

36. Jamieson DJ and Steege JF. The association of sexual abuse with pelvic pain complaints in a primary care population. Am J Obstet Gynecol. 1997 Dec;177(6):1408-12.

37. Walling MK, O'Hara MW, Reiter RC, et al. Abuse history and chronic pain in women: II. A multivariate analysis of abuse and psychological morbidity. Obstet Gynecol. 1994 Aug;84(2):200-6.

38. Walling MK, Reiter RC, O'Hara MW, et al. Abuse history and chronic pain in women: I. Prevalences of sexual abuse and physical abuse. Obstet Gynecol. 1994 Aug;84(2):193-9.

39. Collett BJ, Cordle CJ, Stewart CR, et al. A comparative study of women with chronic pelvic pain, chronic nonpelvic pain and those with no history of pain attending general practitioners. Br J Obstet Gynaecol. 1998 Jan;105(1):87-92.

40. Lampe A, Doering S, Rumpold G, et al. Chronic pain syndromes and their relation to childhood abuse and stressful life events. J Psychosom Res. 2003 Apr;54(4):361-7.

41. Lampe A, Solder E, Ennemoser A, et al. Chronic pelvic pain and previous sexual abuse. Obstet Gynecol. 2000 Dec;96(6):929-33.

42. Toomey TC, Seville JL, Mann JD, et al. Relationship of sexual and physical abuse to pain description, coping, psychological distress, and health-care utilization in a chronic pain sample. Clin J Pain. 1995 Dec;11(4):307-15.

43. Zondervan KT, Yudkin PL, Vessey MP, et al. Patterns of diagnosis and referral in women consulting for chronic pelvic pain in UK primary care. Br J Obstet Gynaecol. 1999 Nov;106(11):1156-61.

44. Howard Fred M. Treatment of chronic pelvic pain in women. UpToDate. 2010;Feb 17, 2011.

45. Howard Fred M. Evaluation of chronic pelvic pain in women. UpToDate. 2011(April 9, 2010).

46. International pelvic Pain Society. History and physical form. Available from: www.pelvicpain.org/resources/handpform.aspx.

47. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977 Apr 8;196(4286):129-36.

48. Howard FM, El-Minawi AM and Sanchez RA. Conscious pain mapping by laparoscopy in women with chronic pelvic pain. Obstet Gynecol. 2000 Dec;96(6):934-9.

49. Daniels J, Gray R, Hills RK, et al. Laparoscopic uterosacral nerve ablation for alleviating chronic pelvic pain: a randomized controlled trial. JAMA. 2009 Sep 2;302(9):955-61.

50. Winkel CA. Role of a symptom-based algorithmic approach to chronic pelvic pain. Int J Gynaecol Obstet. 2001 Sep;74 Suppl 1:S15-20.

51. Price J, Farmer G, Harris J, et al. Attitudes of women with chronic pelvic pain to the gynaecological consultation: a qualitative study. BJOG. 2006 Apr;113(4):446-52.

52. Carlson KJ, Miller BA and Fowler FJ, Jr. The Maine Women's Health Study: II. Outcomes of nonsurgical management of leiomyomas, abnormal bleeding, and chronic pelvic pain. Obstet Gynecol. 1994 Apr;83(4):566-72.

53. Carlson KJ, Miller BA and Fowler FJ, Jr. The Maine Women's Health Study: I. Outcomes of hysterectomy. Obstet Gynecol. 1994 Apr;83(4):556-65.

54. Stovall TG, Ling FW and Crawford DA. Hysterectomy for chronic pelvic pain of presumed uterine etiology. Obstet Gynecol. 1990 Apr;75(4):676-9.

55. Kjerulff KH, Langenberg PW, Rhodes JC, et al. Effectiveness of hysterectomy. Obstet Gynecol. 2000 Mar;95(3):319-26.

56. Kjerulff KH, Rhodes JC, Langenberg PW, et al. Patient satisfaction with results of hysterectomy. Am J Obstet Gynecol. 2000 Dec;183(6):1440-7.

57. Hillis SD, Marchbanks PA and Peterson HB. The effectiveness of hysterectomy for chronic pelvic pain. Obstet Gynecol. 1995 Dec;86(6):941-5.

58. Lee NC, Dicker RC, Rubin GL, et al. Confirmation of the preoperative diagnoses for hysterectomy. Am J Obstet Gynecol. 1984 Oct 1;150(3):283-7.

59. Steege JF. Indications for hysterectomy: have they changed? Clin Obstet Gynecol. 1997 Dec;40(4):878-85.

60. Ortiz DD. Chronic pelvic pain in women. Am Fam Physician. 2008 Jun 1;77(11):1535-42.

61. Owens DK, Lohr KN, Atkins D, et al. Grading the Strength of a Body of Evidence When Comparing Medical Interventions. 2008.

62. Lamvu G, Williams R, Zolnoun D, et al. Long-term outcomes after surgical and nonsurgical management of chronic pelvic pain: one year after evaluation in a pelvic pain specialty clinic. Am J Obstet Gynecol. 2006 Aug;195(2):591-8; discussion 598-600.

63. Sator-Katzenschlager SM, Scharbert G, Kress HG, et al. Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. Wien Klin Wochenschr. 2005 Nov;117(21-22):761-8.

64. Williams RE, Hartmann KE, Sandler RS, et al. Prevalence and characteristics of irritable bowel syndrome among women with chronic pelvic pain. Obstet Gynecol. 2004 Sep;104(3):452-8.

65. Chung MH and Huh CY. Comparison of treatments for pelvic congestion syndrome. Tohoku J Exp Med. 2003 Nov;201(3):131-8.

66. Peters AA, van Dorst E, Jellis B, et al. A randomized clinical trial to compare two different approaches in women with chronic pelvic pain. Obstet Gynecol. 1991 May;77(5):740-4.

67. Williams RE, Hartmann KE, Sandler RS, et al. Recognition and treatment of irritable bowel syndrome among women with chronic pelvic pain. Am J Obstet Gynecol. 2005 Mar;192(3):761-7.

68. Stratton P, Sinaii N, Segars J, et al. Return of chronic pelvic pain from endometriosis after raloxifene treatment: a randomized controlled trial. Obstet Gynecol. 2008 Jan;111(1):88-96.

69. Montenegro ML, Mateus-Vasconcelos EC, Rosa ESJC, et al. Postural changes in women with chronic pelvic pain: a case control study. BMC Musculoskelet Disord. 2009;10:82.

70. Pitts MK, Ferris JA, Smith AM, et al. Prevalence and correlates of three types of pelvic pain in a nationally representative sample of Australian women. Med J Aust. 2008 Aug 4;189(3):138-43.

71. Johnson NP, Farquhar CM, Crossley S, et al. A double-blind randomised controlled trial of laparoscopic uterine nerve ablation for women with chronic pelvic pain. BJOG. 2004 Sep;111(9):950-9.

72. Ling FW. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. Pelvic Pain Study Group. Obstet Gynecol. 1999 Jan;93(1):51-8.

73. Vercellini P, Trespidi L, Colombo A, et al. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril. 1993 Jul;60(1):75-9.

74. Gestrinone versus a gonadotropin-releasing hormone agonist for the treatment of pelvic pain associated with endometriosis: a multicenter, randomized, double-blind study. Gestrinone Italian Study Group. Fertil Steril. 1996 Dec;66(6):911-9.

75. Saravelos HG, Li TC and Cooke ID. An analysis of the outcome of microsurgical and laparoscopic adhesiolysis for chronic pelvic pain. Hum Reprod. 1995 Nov;10(11):2895-901.

76. Karp BI, Sinaii N, Nieman LK, et al. Migraine in women with chronic pelvic pain with and without endometriosis. Fertil Steril. 2010 Dec 8.

77. Fenton BW, Durner C and Fanning J. Frequency and distribution of multiple diagnoses in chronic pelvic pain related to previous abuse or drug-seeking behavior. Gynecol Obstet Invest. 2008;65(4):247-51.

78. Paulson JD and Delgado M. The relationship between interstitial cystitis and endometriosis in patients with chronic pelvic pain. JSLS. 2007 Apr-Jun;11(2):175-81.

79. Tu FF, As-Sanie S and Steege JF. Prevalence of pelvic musculoskeletal disorders in a female chronic pelvic pain clinic. J Reprod Med. 2006 Mar;51(3):185-9.

80. Bodden-Heidrich R, Kuppers V, Beckmann MW, et al. Psychosomatic aspects of vulvodynia. Comparison with the chronic pelvic pain syndrome. J Reprod Med. 1999 May;44(5):411-6.

81. Rein DB, Kassler WJ, Irwin KL, et al. Direct medical cost of pelvic inflammatory disease and its sequelae: decreasing, but still substantial. Obstet Gynecol. 2000 Mar;95(3):397-402.

82. Verit FF, Verit A and Yeni E. The prevalence of sexual dysfunction and associated risk factors in women with chronic pelvic pain: a cross-sectional study. Arch Gynecol Obstet. 2006 Aug;274(5):297-302.

83. Swank DJ, Swank-Bordewijk SC, Hop WC, et al. Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-centre trial. Lancet. 2003 Apr 12;361(9365):1247-51.

84. Palomba S, Russo T, Falbo A, et al. Laparoscopic uterine nerve ablation versus vaginal uterosacral ligament resection in postmenopausal women with intractable midline chronic pelvic pain: a randomized study. Eur J Obstet Gynecol Reprod Biol. 2006 Nov;129(1):84-91.

85. Abbott JA, Jarvis SK, Lyons SD, et al. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. Obstet Gynecol. 2006 Oct;108(4):915-23.

86. Heyman J, Ohrvik J and Leppert J. Distension of painful structures in the treatment for chronic pelvic pain in women. Acta Obstet Gynecol Scand. 2006;85(5):599-603.

87. Vercellini P, Barbara G, Somigliana E, et al. Comparison of contraceptive ring and patch for the treatment of symptomatic endometriosis. Fertil Steril. 2010 May 1;93(7):2150-61.

88. Zupi E, Marconi D, Sbracia M, et al. Add-back therapy in the treatment of endometriosis-associated pain. Fertil Steril. 2004 Nov;82(5):1303-8.

89. Vercellini P, De Giorgi O, Oldani S, et al. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol. 1996 Aug;175(2):396-401.

90. Parazzini F, Di Cintio E, Chatenoud L, et al. Estroprogestin vs. gonadotrophin agonists plus estroprogestin in the treatment of endometriosis-related pelvic pain: a randomized trial. Gruppo Italiano per lo Studio dell'Endometriosi. Eur J Obstet Gynecol Reprod Biol. 2000 Jan;88(1):11-4.

91. Onwude JL, Thornton JG, Morley S, et al. A randomised trial of photographic reinforcement during postoperative counselling after diagnostic laparoscopy for pelvic pain. Eur J Obstet Gynecol Reprod Biol. 2004 Jan 15;112(1):89-94.

92. Ghaly AFF. The psychological and physical benefits of pelvic ultrasonography in patients with chronic pelvic pain and negative laparoscopy. A random allocation trial. Journal of Obstetrics & Gynaecology. 1994;14:269-271.

93. Ye ZQ, Cai D, Lan RZ, et al. Biofeedback therapy for chronic pelvic pain syndrome. Asian J Androl. 2003 Jun;5(2):155-8.

94. Williams RE, Hartmann KE and Steege JF. Documenting the current definitions of chronic pelvic pain: implications for research. Obstet Gynecol. 2004 Apr;103(4):686-91.

95. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008 Feb;9(2):105-21.

96. Gallagher RM. Biopsychosocial pain medicine and mind-brain-body science. Phys Med Rehabil Clin N Am. 2004 Nov;15(4):855-82, vii.

97. Hyams JS. Irritable bowel syndrome, functional dyspepsia, and functional abdominal pain syndrome. Adolesc Med Clin. 2004 Feb;15(1):1-15.

98. Ong KS and Keng SB. The biological, social, and psychological relationship between depression and chronic pain. Cranio. 2003 Oct;21(4):286-94.

99. Turk DC and Okifuji A. Psychological factors in chronic pain: evolution and revolution. J Consult Clin Psychol. 2002 Jun;70(3):678-90.

100. Grace VM. Pitfalls of the medical paradigm in chronic pelvic pain. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000 Jun;14(3):525-39.

101. Turner JA, Deyo RA, Loeser JD, et al. The importance of placebo effects in pain treatment and research. JAMA. 1994 May 25;271(20):1609-14.

102. Moore RA, Gavaghan D, Tramer MR, et al. Size is everything--large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. Pain. 1998 Dec;78(3):209-16.

103. Andrews J. Vulvodynia management: an evidence-based approach. J Clin Outcomes Manage 2010;17(5):225-238.

104. Bradford A and Meston C. Correlates of placebo response in the treatment of sexual dysfunction in women: a preliminary report. J Sex Med. 2007 Sep;4(5):1345-51.

105. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995 Feb 1;273(5):408-12.

106. Johnson AG. Surgery as a placebo. Lancet. 1994 Oct 22;344(8930):1140-2.

107. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002 Jul 11;347(2):81-8.

Acronyms and Abbreviations

ADL	Activities of daily living
AHRQ	Agency for Healthcare Research and Quality
BDI	Beck Depression Inventory
CI	Confidence interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CPP	Noncyclic chronic pelvic pain
EPC	Evidence based Practice Center
EQ VAS	EuroQol Visual Analog Scale
EQ-5D	EuroQol-5D
FSD	Female sexual dysfunction
g,G	Group
GnRH	Gonadotropin releasing hormone
IBS	Irritable bowel syndrome
IC	Interstitial cystitis
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
KQ	Key question
LUNA	Laparoscopic utero-sacral nerve ablation
MPQ	McGill Pain Questionnaire
MRI	Magnetic resonance imaging
n, N	Number
NR	Not reported
nRCT	Nonrandomized controlled trial
OCP	Oral contraceptive pills
OR	Odds ratio
PBS	Painful bladder syndrome
PET	Positron Emission Tomography
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
SERM	Selective estrogen receptor modulator
SOE	Strength of evidence
TENS	Transcutaneous Electrical Nerve Stimulation
TEP	Technical Expert Panel
VAS	Visual analog scale