Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of Therapies for Women with Noncyclic Chronic Pelvic Pain*

Draft review available for public comment from May 26, 2011 to June 23, 2011.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1	Executive Summary	The inconclusive findings are disappointing and even troubling. Given the array of surgical/invasive interventions designed to manage this problem, the lack of superior documented outcomes with any approach should be emphasized more strongly.	We have strengthened these statements in the executive summary and conclusions sections of the review.
Public Reviewer #2	Executive Summary	Mechanical Pelvic pain referred from the sacroiliac joint(s) is a common pain generator, that is poorly diagnosed or treated, without specific training. As odd as it may sound I have thoroughly enjoyed treating chronic pelvic pain and can usually have these ladies back to their normal lives in 1 or 2 clinic visits. You will not find this on your usual literature search. I have treated approx 30K patients with these sorts of disorders.	Thank you for pointing this out. One study in the current review did indicate that a number of women with CPP had sacroiliac pain (Droz et al., 2011).
Public Reviewer #2	Introduction	Pelvic pain is an area of medicine that I have specialized in for nearly 20 years, in particular the dynamics and pain referral of the Sacroiliac Joint (SI). However the paper that I had sent into the American Family Physician, was rejected in 2001 and I just shelved it and kept taking care of patients..(or I was deployed or overseas.. or...) Through trauma of some kind that includes childbirth, MVAs and/or significant of trivial falls can shift one or both the SI joints and cause a pain picture like the enclosed file. Often the leg lengths will be altered and the pelvis becomes torqued.. which is very simple to do just with physical examination. Unfortunately most physicians do not know how to attempt this maneuver. Treatment is also fairly simple and their pain is gone or reduced.. the very economical diagnosis and treatment completely patient centric.	Thank you for your comments.
Peer Reviewer #2	Introduction	The section is well done (barring some typos) and far more thorough, thoughtful, and frank than most papers in the field (which are reluctant to note the lack of evidence or efficacy for many interventions). I do take issue, however, with the lack of clear statement that the guidelines from ACOG on an empirical trial of GnRH agonists was industry-driven and not based on an independent expert review.	The focus of the current review is on the effectiveness of therapies for CPP. Thus we did not review the quality of the guideline; the introduction is simply that – introducing the report user to the background of science and clinical practice that exists at the time that the review was undertaken.
Peer Reviewer #3	Introduction	Well written	Thank you for your comments.
Peer Reviewer #4	Introduction	The introduction was informative and concise. I did think that the authors should be more critical in the section relating to comorbidities. The strength of the relationship between CPP and the various psychological factors listed (pg. 2, lines 41-57) and abuse is not as accepted as the report suggests. The majority of studies which have assessed these factors are methodologically weak. I am sure that the authors are more than aware of this, but it woould enhance the report if the critique was strengthened in this section.	Thank you for your comment. We have altered this section to note that CPP has been suggested to be associated with various gynecologic and psychological factors.

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Peer Reviewer #5	Introduction	Have no comment. The team has done an excellent job reviewing what is known, framing the gap particularly in light of current standard of care which is often surgical with no data.	Thank you for your comments.
Peer Reviewer #6	Introduction	The introduction well describes the broadness of this topic and many of the issues in reviewing the literature.	Thank you for your comments.
Public Reviewer #1	Methods	I see many patients who utilize eastern medicine practices, CAM, accupuncture. Something to consider in nonpharmalogic or alternate options in regards to further research needed	We have noted a need for further research into nonpharmacologic and nonsurgical management approaches in the future research section of the report.
Public Reviewer #1	Methods	While I agree with the search methods, the dismal, inconclusive findings might have prompted a broader search. Surely, CPP is not managed surgically in all parts of the world. One might even question its prevalence in other nations. Is this somehow unique to the US or just uniquely managed.	Our search strategy was deliberately quite broad and included searches in multiple databases as well as scanning of the reference lists of included studies. The report also includes the literature meeting our criteria and addressing non-surgical interventions. As we note in the future research section of the report, more research is needed into non-surgical and non-pharmacologic approaches.
Public Reviewer #2	Methods	Orthopedic Medicine/Manual Medicine/Osteopathic Medicine treatment... very specific diagnosis and treatment.. To date I have taught approx 325 physicians in these techniques. This particular treatment may be seen in the pelvic portion of the a course I teach http://www.usafp.org/USAFP-Lectures/2007-Lectures/15%20March%20-%20Thursday/Jorgenson-USAFP%20Ortho%20Med%202007.pdf	Thank you for your comments.
Peer Reviewer #2	Methods	Methodology was very competent and thorough.	Thank you for your comments.
Peer Reviewer #3	Methods	Good search strategy. I am amazed how much of the published research had to be excluded, however, exclusion / inclusion criteria are well defined and appropriate.	Thank you for your comments.
Peer Reviewer #4	Methods	The methods are robust, and the inclusion/exclusion criteria are justified. The search strategy is clear, however, I could not find justification for the time frame - what was the rationale for starting the searches in 1990?	The report notes in the Methods section that "We limited searches to the English language and literature published since 1990, when laparoscopic techniques became more widely used."
Peer Reviewer #4	Methods	It was also not clear why the authors did not include ongoing trials - whilst I realise they would not necessarily be able to provide evidence they are useful in assessing the direction of current research.	EPC methods for systematic reviews do not include studies for which results are not yet available; however, we have included an appendix of ongoing CPP trials located in the clinicaltrials.gov database and EU trials register.
Peer Reviewer #4	Methods	The statistical methods are appropriate and fit for purpose. The sample size calculations provided were particularly helpful. The process of quality assessment was clear and well thought through. Overall, the methods are very robust. good.	Thank you for your comments.

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Peer reviewer #5	Methods	The exclusion/inclusion criteria well justified. Further more, in light of paucity of data and conventional clinical practice, the team has done an excellent job of summerizing data (despite lack of sound methodological) that are in current clinical use. In that spirit, I would like to see some comment about the surgical approach of "periscarcal neurectomy' that is in practice. The reviewer acknowleges that the data would be even more meger than the one on LUNA. However, in light of negative findgins in LUNA, most docs are now suggesting perisacral neurectomy which has a much greater morbidity. This procedure is unlikely to make the first level of cut (subjects # 50 and greater), but is highly utilized in clinical practice and is of great public health concern in light of associated morbidity (e.g. bowel dysfunction, and surgical complication). A limited discussion of this procedure which is gaining popularity is unlikely to add but a few sentence to the report but has great impact in policy level and decision process.	We sought evidence about Presacral Neurectomy (PSN) (listed on page 3 under the Interventions paragraph) but did not locate studies meeting our criteria. We have added a specific statement in the Results chapter that we did not locate studies of PSN that met our inclusion criteria.
Peer reviewer #6	Methods	The inclusion and exclusion criteria are justifiable. The search strategies are explicitly stated and logical. The definitions or diagnostic criteria for the outcome measures seem appropriate. The statistical methods used also appear to be appropriate.	Thank you for your comments.
Peer reviewer #6	Methods	In the area on page 21 which describes the grading of the evidence for each key question, it is not clear what precise and imprecise refer to.	We have added a table describing EPC definitions of these domains to the Methods section.
Peer reviewer #6	Methods	Also unclear is what consistent and inconsistent refer to.	We have added a table describing EPC definitions of these domains to the Methods section.
Public Reviewer #2	Results	Better than 86% of patients are pain free in 1.8 clinic visits.	Thank you for your comments.
Peer Reviewer #2	Results	This very thorough analysis and report on the selected studies and selected results is greatly appreciated. I do think the point should be more strongly made that it is extremely difficult to compare surgical studies because of variability of surgical skills	Thank you for your comment. We have emphasized this point in the report's Discussion section.
Peer Reviewer #3	Results	Yes all excellent.	Thank you for your comments.

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Peer Reviewer #4	Results	The results are clear and well presented. Although, reading Fig. 1 (pg. 23) I did wonder about the high number of studies (n=548) excluded due to low sample size. It would be of interest (but outside the scope of this review) to know something about the direction of effects.	As the report notes in the Methods section, we set a sample size cut off of 50 for treatment studies and 100 for studies reporting on harms or comorbidities in order to ensure that the studies included in the review were of adequate power to contribute meaningful data. Even using a generous sample size requirement of 50, few studies included enough participants. We have noted in the future research section of the report that ongoing studies should include larger samples.
Peer Reviewer #4	Results	The key messages are highlighted throughout the section. Tables are clear and well formatted. However, where comparison groups are reported (e.g. Table 9) the way the groups were labeled was confusing - this made this table difficult to read.	Thank you for your comments; we tried to balance a concise presentation with clarity in the tables and hope that formatting changes help with readability.
Peer Reviewer #5	Results	I very much appreciated details provided in appendix B in rational for exclusion of specific study.	Thank you for your comments.
Peer reviewer #6	Results	The amount of detail in the results section is appropriate. The key messages are explicit. The figures, tables and appendices are adequate and descriptive.	Thank you for your comments.
Peer reviewer #6	Results	On the top of page 37, in the first full paragraph, the time interval for reduction in days is not well described. Is this a reduction in days over a one month time?	We have clarified this statement in the Results section.
Peer reviewer #6	Results	Page 41, table 10 Assessment in the Stratton study was 18 months after patient completed 6 months of treatment rather than 12 months after patient completed 6 months of treatment	We have clarified this statement in the Results section.
Peer reviewer #6	Results	Page 56 Many of the studies are rated as inconsistent, but to this reviewer it is unclear what inconsistent refers to.	We have added a table describing EPC definitions of these domains to the Methods section.
Public Reviewer #2	Discussion	SI joint is a significant pain generator of chronic pelvic pain. At the very least, if radiologic studies are negative, there is no infectious cause, SI joint (and at times a subluxed coccyx) is a frequent culprit and often easily reduced and/or eliminated as a cause in clinic without expense tests. We are currently working on a provider training program that will hopefully start in early winter for the US Navy though BUMED and the Wounded Warrior program. Would prefer to not have my email addresses advertised outside of US Govt/MHS.	Thank you for your comments. We hope to read more about your approaches.
Peer Reviewer #2	Discussion	Conclusions are straight forwardly stated. The future research section is particularly important.	Thank you for your comments.

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Peer Reviewer #3	Discussion	Yes, main message that I got is that CPP is: very prevalent no good algorithm is available for evaluation poorly defined poorly researched	Thank you for your comments.
Peer Reviewer #4	Discussion	The discussion was clear and followed a logical format. The summary tables are very helpful. The limitations of the included studies are adequately addressed. Given the inclusion/exclusion criteria I could not identify any missing studies. The direction for future research is clearly stated. The suggestions for future research can be readily translated by a range of researchers (hopefully working together) towards a more holistic, yet evidence based, approach to treatment and healthcare for women with CPP.	Thank you for your comments.
Peer Reviewer #5	Discussion	None appreciated	Thank you for your comments.
Peer Reviewer #6	Discussion	With regards to etiology, it is difficult to infer causality in studies so an analysis of the distribution of the underlying "causes" of CPP does not seem, to this reviewer, to be a possible research strategy. One approach might be to encourage translational science to systematically assess the relation between pain and different diseases much the way Karen Berkley has done with the endo Rat model and endometriosis.	We agree that this is a difficult issue but feel that determining etiology is important. We have added a statement noting the value of basic science/translational approaches in investigating causal factors to the Discussion section of the report.
Peer Reviewer #6	Discussion	Similarly, while it seems a laudable goal to identify subgroups at risk of chronic pelvic pain, it is unclear how one would go about conducting these sorts of longitudinal studies.	While it is beyond the scope of the current report to outline methods for conducting future research in the areas indicated, we concur that how such studies are designed will be critically important.
Peer Reviewer #6	Discussion	Including research to delineate iatrogenic pain is an important goal. Not considered here is the fact that surgical strategies to treat chronic pelvic pain may, in fact, result in nervous system changes which perpetuate chronic pelvic pain. An example might be damaging pelvic nerves during surgery as might arise from thermal energy used.	Thank you for your comment. We agree that iatrogenic pain is an important area to consider in CPP and have added text to emphasize potential surgical harms to the Discussion section.
Peer Reviewer #6	Discussion	The standardization of definitions and diagnostic criteria seems to be the most important research goal to be attained. As this review clearly points out, the clinical signs and diagnostic criteria to assess and define chronic pelvic pain are missing from studies as is analgesic use.	Thank you for your comments.

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Peer Reviewer #6	Discussion	Diagnostic approaches and standardized outcome measures are also needed. It is important to assure that the disease observed with pain is, in fact, the reason for the pain. This is very difficult to determine but one might, in the case of endometriosis for example, remove endometriosis lesions and determine if pain is diminished before employing an intervention.	Thank you for your comments.
Peer Reviewer #6	Discussion	The part of the discussion regarding future interventions seems thorough but might be enhanced if more complex designs are embraced which mirror real life (going on to another treatment after one fails, for example).	We have expanded our discussion to note that future research should consider various study designs as well.
Peer Reviewer #6	Discussion	Assessing the benefits of surgical treatment is more complex than this review suggests. In the case of endometriosis, for example, there is a variable appearance of lesions, the diagnostic criteria for lesions as well as the surgical approach to treating lesions (destroyed in place or removed), whether adhesions are cut or removed or when in the menstrual cycle surgery is performed. Each of these issues must be standardized. These are difficult to standardize and require multicenter studies.	We agree that assessing surgical benefits is complex and have added a statement in the Discussion section that surgical approaches should be standardized and studies should use multi-center designs.
Public Reviewer #2	References	http://www.usafp.org/USAFP-Lectures/2007-Lectures/15%20March%20-%20Thursday/Jorgenson-USAFP%20Ortho%20Med%202007.pdf	Thank you for pointing out this reference.
Peer Reviewer #1	General	AUA clinical leaders have reviewed the draft CER on Noncyclic Chronic Pelvic Pain in Women and have no revisions to suggest. We would like to make you aware of recent AUA Guidelines (2011) on the Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome<http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/ic-bps/diagnosis_and_treatment_ic-bps.pdf> Interstitial Cystitis Treatment Algorithm<http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/ic-bps/ic_treatment_algorithm.pdf>	Thank you for pointing out these reports. We have referenced the guideline in the review's introduction.

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Peer Reviewer #2	General	Generally, the aims of this report are valuable, particularly to assist practitioners and patients, as well as other stakeholders, in a very difficult treatment area such as chronic pelvic pain. The authors have approached their topic with admirable thoroughness. However, there are some basic assumptions that are not well-explained and therefore leave the reader confused. Most especially, since the report notes that a frequently diagnosed etiology is endometriosis, the authors never explain how they determine which of the studies of patients with endometriosis tease out non-cyclic chronic pelvic pain or non-cyclic / mixed chronic pelvic pain symptoms. It is not clear to me if the authors are including endometriosis, for example, as automatically part of this category even though many studies do not clearly specify that. Typically, endometriosis studies would define endometriosis as the presence of glands and stroma without noting whether patients had non-cyclic / mixed pain.	We included all studies that reported data about subjects with noncyclic CPP; many of these subjects also had confirmed endometriosis. As described in the report's Methods section, if the focus of a study was endometriosis, we examined the publication to determine if there was data about noncyclic CPP and only included those studies including women with noncyclic CPP that also met our other inclusion criteria.
Peer Reviewer #2	General	In general, I believe the report is far too confusing to be greatly useful to most practitioners or patients. This may, indeed, reflect the state of knowledge as well as the state of current studies on CPP.	While the majority of reviewers felt that the report was clearly presented, we have worked to clarify statements throughout the report. We also note that the AHRQ's Eisenberg Center will be preparing translational materials for clinicians and consumers to help disseminate the key points of the report.
Peer Reviewer #3	General	The report is excellent and much needed info to determine where we need to focus our research. The key questions are specific and well written.	Thank you for your comments.
Peer Reviewer #4	General	The report is extensive and well thought through. The report is clinically meaningful, although I would add that this is restricted to the population under study i.e. mainly women referred to secondary/ specialist care. The key questions are appropriate and explicitly stated. However, given the limited research in this area it is perhaps not surprising that KQ3 and KQ5 were not supported by evidence.	Thank you for your comments. We have emphasized statements about the applicability of the findings in the Summary section of the report.
Peer Reviewer #5	General	Very well written and organized review. This review does an amazing job in framing the problem in a very difficult and poorly research area.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	General	This report is one of the most thorough and best reviews that I have ever read on this topic. The authors have identified many shortcomings in the literature and clearly articulate information that is sorely needed. As it is a clinical outcomes paper, it does not address or recognize some of the recent advances noted in defining the relationship between pain, the central nervous system, and certain diseases. However, it nicely straddles the issues of clinical treatments and disease and pain, and thus is an important piece of work. Importantly, the authors comment on the lack of standardized assessments of chronic pelvic pain and the general reliance on patient reported information. Developing objective findings for clinical endpoints is an important methodological issue. This report is clinically meaningful. The target population and audience are explicitly defined. In general, the key questions are appropriate and explicitly stated.	Thank you for your comments.
Peer Reviewer #6	General	Question 1: Prevalence of comorbidities The prevalence of comorbidities is a very complex topic. There is some evidence that having two co-morbidities may heighten pain and dysfunction (Giamberardino, 2010). Thus the prevalence of comorbidities may better define the population studied, to avoid categorizing someone as chronic pelvic pain when the pain is more global (as in fibromyalgia), to recognize co-morbidities which may be secondary endpoints (like irritable bowel or painful bladder), or to recognize co-morbidities which may be important contributors to pain like depression and anxiety. These are all important facets of research and contribute to making this area difficult to study. It might be wise to convey which or all of these issues are the goal of the question. It is important to have consistent criteria for defining the diseases or conditions themselves as well as co-morbidities in intervention studies.	Thank you for your comments. We have added text to the report's introduction expanding on issues related to comorbidities.

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Peer Reviewer #6	General	Question 3 Evidence for differences in surgical outcomes by etiology This question does not mirror what is done in clinical practice or research. Thus it is not surprising that no studies were found to address the issue of determining an etiology of pain after surgery. The reason for not finding an etiology after surgery is because, as the authors point out later in their document, there is an assumption that pain is gynecologic and often endometriosis related. If endometriosis is not found at surgery, the surgeon often assumes that the pain is not gynecologic. This assumption hampers the standardization of gathering and reporting on information that would be helpful in determining the reason for pain in women who do not have gynecologic causes or who may have other co-morbidities. Furthermore, there has been a shift in practice to empirically treating women with hormonal agents which has resulted in a shift away from surgery in the United States. This further hampers answering this question.	Thank you for your comments. We have emphasized the need for a better understanding of etiology and thorough diagnostic work-up in the report's future research section.
Peer reviewer #6	General	Question 5 Selecting one intervention over another In studies of pain in general and for gynecologic causes specifically, most studies are designed to include subjects who present with pain in which an intervention is tested and compared either to another intervention or a placebo. Currently, clinical trial design does not offer a clear plan to offer an alternative intervention if the first intervention fails. That results in studies that are not generalizable to the general population, that overestimate (often with insufficient power) effectiveness, and have high loss to follow-up (what woman would stay in a study of a treatment that isn't working for her). The authors get at this issue but could address this more in the discussion. In the recent pain consortium meetings at the NIH, some have suggested a novel design in which a sequence of interventions is planned in the study design.	Thank you for your comments. We agree that typical study designs are currently insufficient for addressing this issue and have strengthened that point in the Discussion section.
Peer Reviewer #2	Clarity/ usability	Unfortunately, the report is difficult to use – certainly clinicians and patients will find it generally unhelpful. What could make it more helpful would be a statement of some important general concepts in an executive summary or separate summaries for clinicians and patients (just key points).	We have added a summary of key points to the Executive Summary. As noted, the AHRQ's Eisenberg Center will also be preparing clinician and consumer guides that will encapsulate the report's key findings for these audiences.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Clarity/ usability	The conclusions were robust and well situated within the findings from the review. The findings were not over hyped and the authors contextualised their findings well - not easy to do given the low evidence base. The authors should be commended for their synthesis and appraisal of the evidence. The report does not offer practitioners easy answers to their clinical questions - rather it poses more! This is not a criticism merely a comment on the lack of high quality research in this area. However the findings will certainly inform policy and future research, which is clearly urgently needed. One would hope that a report of this magnitude would encourage future research in this area.	Thank you for your comments. We concur that more research is needed and hope that the report lays out some directions for that.
Peer reviewer #6	Clarity/ usability	The report is well structured and organized. With the poor state of evidence in this area, it is hard to imagine how the conclusions can be used to inform policy or practice decisions. It seems likely that this document can be used to improve the criteria for research	Thank you for your comments. We hope that the report will contribute to improving research to inform decision making in this area.
Peer reviewer #3	Clarity/ usability	Yes, well structured, easy to read, comprehensive and can be used to inform important decisions.	Thank you for your comments.
Peer reviewer #5	Clarity/ usability	Very precise and an excellent example of how to present a focused overview of a very difficult area of inquiry	Thank you for your comments.