D.10 Pharmacological, non-pharmacological, surgical and combination management strategies

D.10.1 Network meta-analysis for women presenting with pain as their primary concern

Item	Details
Review question	**What is the effectiveness of the following treatments for pain relief endometriosis, including recurrent and asymptomatic endometriosis:** • Hormonal medical treatments • Surgery • Non-pharmacological treatments • Combinations of surgery plus hormonal treatments?

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Item	Details
Objective	The aim of this NMA is to determine the clinical efficacy of treatments in women with endometriosis.
Population	Women between menarche and menopause with endometriosis or suspected endometriosis of any stage or severity who are experiencing pain. Suspected endometriosis may be based on the history of the patient, pelvic examination, and other tests such as ultrasound, MRI and the CA-125 blood test. Studies with indirect populations (such as women with dysmenorrhea, women with non-confirmed pelvic pain, or post-menopausal women) will not be considered Exclusions: • women with chronic pelvic pain which was known to be due to causes other than endometriosis • Use of hormonal therapies (excluding depot medroxyprogesterone) in the previous 1 month • Use of depot medroxyprogesterone in the previous 6 months Those suspected based solely on a CA-125 test with no other contributing factor, CA-125 should be used in combination with other evaluative measures.
Stratified analyses	
Subgroup Analyses	Networks will be examined separately if study populations for separate groups of treatments are substantially different: • Hormonal treatments • Surgical treatments • Non-pharmacological treatments Other subgroup analyses • Type of diagnosis of endometriosis (e.g. endometrioma) • Types of pain
Covariates	Covariates can sometimes be included to reduce heterogeneity instead of running subgroup analyses, where data is available. In order of importance (where data are available): • Type of disease (ovarian, peritoneal, deep) • Stage of endometriosis • Prior surgery within the last 6 months ○ Not including diagnostic surgery if separately defined by study ○ Not including surgery immediately (within 4 weeks) prior (combined surgery + hormonal therapy) • Bias (e.g. blinding) • Age • BMI • Associated heavy menstrual bleeding
Interventions	**All interventions in the following classes (in bold) will be considered, provided doses are within ranges specified by the Committee (as below) or those within the BNF.** **Hormonal Medical Treatments** ***Danazol/gestrinone*** Danazol • High dose (400-800mg/d) • Low dose (100-400mg/d) Gestrinone

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	Oestrogens Oestradiol (oral – 1-2mg/d) Conjugated equine oestrogens (CEE) (oral – 0.3-1.25mg/d) ***Progestogens*** Lynestrenol Norethindrone (norethisterone) (2.5mg/d) Gestodene (i.m 5-10mg) Desogestrel (oral – 75ug/d) Medroxyprogesterone • Low dose oral (15-20mg/d) • High dose oral (20-30mg/d) • i.m (150mg/3m) • s.c. (104mg/3m) Levonorgestrel • Oral (30ug/d) • Mirena coil (20ug/d released over 5 years) Promegestone (s.c. – 68mg released over 3 years) Dienogest (2mg/d) – *Not available in BNF but will be used to provide evidence of class efficacy* ***GnRH agonists*** Nafarelin (nasal spray – 200ug/12h) Leuprorelin acetate (depot – 3.75mg/m) Goserelin (s.c – 3.6mg/m) Triptorelin (dipherelin) (i.m – 3mg/m) Buserelin (300ug/8h) ***Anti-androgens/Progestogens*** Cyproterone acetate (10-12.5mg/d) *(only in combination as COC)* ***Aromatase inhibitors*** Anazstrozole (oral – 1mg/d) Letrozole (oral – 2.5mg/d) ***Selective oestrogen receptor modulators*** Raloxifene (60mg/d) ***Selective progestogen receptor modulators*** Tibolone (oral – 2.5mg/d) **Surgical Treatments** ***Excisional laparoscopic surgery*** Laser, diathermy, etc. ***Ablative laparoscopic surgery*** Laser, diathermy, etc.

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Item	Details
	Non-Pharmacological Treatments ***Behavioural medicine*** *(such as psychological and physiotherapy techniques)* • Cognitive behavioural therapy • Mindfulness • Relaxation techniques • Pain management programmes – • Pain management physiotherapy • Pain management psychology • Expert patient programme • Exercise (for example yoga and pilates) • Hypnosis • Pyschosexual therapy • Biofeedback ***Physical methods*** • Acupuncture • (TENS) • Manual and Physical therapy • Massage (e.g. shiatsu) • Osteopathy • Chiropractic treatment • Reflexology ***Other*** • Herbal medicine • Naturopathy • Homeopathic therapy • Nutrition (gluten free, dairy free, vegetarian, endo diet)
Comparisons	• All interventions listed above • Combinations of those interventions • Placebo • No treatment
Outcomes	Primary • Pain (measured by Biberoglu and Behrman scale or other scale with identical subscales): ○ Separated into subscales if data for these are reported separately (non-menstrual pelvic pain, dyspareunia, dysmenorrhea, induration, pelvic tenderness) • Pain measured by a Visual Analogue Scale (VAS) • Quality of life (measured using the SF-36) • Discontinuation of treatment due to adverse effects (surgical studies will not be included for this outcome) The latest time point from each study will be used, up to a maximum duration of 12 months (inclusive) for pain relief and QoL. For discontinuation, maximum duration will depend on whether relative effects change across different study follow-ups: • If no change then we will use a maximum of 12 months (inclusive) and model as OR – this assumes all discontinuation occurs within the first 3 months

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	• If change is found then we will include all study durations and model discontinuation as a rate ratio or HR
Study design	Only RCTS will be considered for inclusion. Both periods of cross over RCTs will be considered if authors have used a suitable paired analysis and if they have tested for carryover effects or have used a suitable washout period. Exclusion criteria: studies with a duration of less than 3 months, studies with less than two relevant treatments (non-relevant treatments include non UK licensed drugs).
Population size and directness	Studies with mixed populations (e.g. mixture of patients with different (but specified) severities) will be considered under the following assumptions: • If more than 2/3 of the sample are within a particular pre-specified strata then we will code the study as including women with this characteristic. Otherwise we will label this characteristic as “mixed”. • Studies must have >15 participants per treatment arm
Review strategy	Synthesis of data • Network meta-analysis will be conducted using Winbugs codes (TSU Bristol Unit) • We will use mean differences for reporting the results of continuous outcomes • We will use the ORs (95% cr.i.) for reporting the results of dichotomous outcomes • We will use rate ratios or HRs for reporting the results of rate outcomes. • We will impute SD (accounting for uncertainty in SD imputation) where it has not been reported and assess impact of this in a sensitivity analysis • We will not use MIDs as outputs will feed directly into HE model so MIDs will not be needed
Model Structure	• Treatments not included in the list of interventions will be included if they provide indirect evidence to the network via a closed loop of treatment effects. • Class effect model to allow borrowing of evidence from other treatments if network is too sparse. The following investigations into which class effect model fits the data best will be performed: ○ Treatments of the same class grouped by route of administration (e.g. orally administered GnRH analogues would be an individual class) ○ Treatments of the same class grouped (e.g. GnRH analogues would be an individual class) • We will test for exchangeability of within-class treatments to assess if a class model is appropriate • We will calculate a composite score of the Biberoglu and Behrman subscales, using a multivariate approach with known correlations between each scale • We will consider a multivariate NMA approach between Biberoglu and Behrman total (composite) score, VAS, and QoL scales and consider a multivariate approach • Adjusted for covariate(s) (severity as primary): ○ For multivariate this requires assuming correlations are same in different covariate subgroups (e.g. more/less severe) • Use empirical priors (if available) where the ratio of studies to treatments is less than 3:1
Assumptions	• Standard NMA assumptions • Means are normally distributed (Central Limit Theorem) • If covariates are included we assume that there is no multiplicative effect of this with the different hormonal therapies (i.e. no interaction terms)

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Sensitivity Analyses	• Treatment characteristics that have not been stratified/subgrouped (e.g. dose – high/low, if there is not enough data for subgroup analysis) • Using studies with mixed populations • Imputed SDs • Priors

D.10.2 Clinical pairwise review

Item	Details
Areas in the scope	• Pharmacological and surgical treatments including analgesics, hormonal medical treatments, neuromodulators, ablation, excision and hysterectomy with or without oophorectomy. • Combining pharmacological and surgical treatments. • Non-pharmacological management specific to pain (for example acupuncture).
Review question in the scope	**Pharmacological and surgical treatments** What is the effectiveness of the following treatments for endometriosis, including recurrent and asymptomatic endometriosis: • analgesics • neuromodulators • **hormonal medical treatments** • **ablation** • **excision** • hysterectomy with or without oophorectomy? **Combinations of treatments** What is the effectiveness of pharmacological therapy before or after surgery compared with surgery alone? **Non-pharmacological management specific to pain** What is the effectiveness of non-pharmacological therapies (for example acupuncture) for managing pain associated with endometriosis?
Review question for the guideline	What is the effectiveness of the following treatments for endometriosis, including recurrent and asymptomatic endometriosis: • Hormonal medical treatments • Ablation • Excision • Combinations of treatments (pharmacological therapy before or after surgery compared to surgery alone) • Non-pharmacological management specific to pain
Objective	The objective of these reviews was to identify effective treatment classes and interventions within hormonal medical treatment and non-pharmacological management of pain, effective surgical techniques and to establish whether and which hormonal medical treatment and surgery combinations are effective.
Population and directness	Inclusions: • women between menarche and menopause with endometriosis of any stage or severity. • women with a suspected diagnosis of endometriosis (definition: suspected diagnosis based on the history of the patient, pelvic examination and other tests such as ultrasound, MRI and the CA-125 blood test) Exclusions:

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	• women with chronic pelvic pain which was known to be due to causes other than endometriosis • those suspected based solely on a CA-125 test with no other contributing factor (CA-125 should be used in combination with other evaluative measures) Studies with indirect populations (such as women with dysmenorrhea, women with non-confirmed pelvic pain, or post-menopausal women) will not be considered.

Intervention	**Hormonal medical treatments**
	of any type and administered at any dose, frequency, treatment duration recommended in the BNF, or by any route of administration:
	• Combined oral contraceptive pill (patch, ring)
	• Progesterone only pill
	• Implant (Nexplanon / Implanon {not available in UK anymore})
	• Injection [Depo-Provera])
	• Levonorgestrel-releasing intrauterine system (LNG-IUS [mirena])
	• High dose progestogens (e.g medroxyprogesterone acetate)
	• Danazol
	• Gonadotrophin-releasing hormone analogues (GnRHa)
	• Antiprogestogens (mifepristone [RU 486])
	• Combined treatment (GnRH agonist with "add back" HRT/Tibolone)
	• Aromatase inhibitors (for example anastrazole, lanastrozole, letrazole and exemestane)
	• Selective oestrogen receptor modulators (SERMs) (tamoxifen, raloxifene)
	• Selective progesterone receptor modulators (SPRMs) (ulipristal, mifepristone)
	
	Surgical interventions
	• Ablation
	• Excision
	• General techniques:
	  ○ Robotic
	  ○ Laparoscopic
	  ○ Open excision
	  ○ Total peritoneal excision
	• Specific techniques:
	  ○ laser
	  ○ diathermy
	  ○ bi-polar and mono polar
	  ○ ultrasonic energy or a combination i.e. ultrasonic with bi-polar)
	• These may also include:
	  ○ Ovarian cystectomy
	  ○ Drainage of endometriosis
	• Exclude: helium coagulation {refer to IPG, no sufficient evidence to use in normal practice}
	
	Combinations of treatments
	• Any hormonal medical treatment administered before, after or both before + after any surgical treatment
	
	Non-pharmacological management specific to pain
	• Behavioural medicine (such as psychological and physiotherapy techniques):
	  ○ Cognitive behavioural therapy

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	○ Mindfulness ○ Relaxation techniques ○ Pain management programmes - ○ Pain management physiotherapy ○ Pain management psychology ○ Expert patient programme ○ Exercise (for example yoga and pilates) ○ Hypnosis ○ Pyschosexual therapy ○ Biofeedback • Physical methods: ○ Acupuncture ○ (TENS) ○ Manual and Physical therapy ○ Massage (e.g. shiatsu) ○ Osteopathy ○ Chiropractic treatment ○ Reflexology • Other: ○ Herbal medicine ○ Naturopathy ○ Homeopathic therapy ○ Nutrition (gluten free, dairy free, vegetarian, endo diet)
Comparison	**For hormonal medical treatments**: • Hormonal medical treatment vs no treatment, usual care or placebo • Hormonal medical treatment A vs Hormonal medical treatment B • Hormonal medical treatment vs other medical treatment • Hormonal medical treatment vs. surgery • Hormonal medical treatment vs. combinations of hormonal medical and surgical treatment **For surgical interventions**: • Surgery compared to diagnostic laparoscopy • Ablation vs excision **For combinations of treatments:** • Hormonal medical treatment before surgery vs no treatment/placebo • Hormonal medical treatment after surgery vs no treatment/placebo • Hormonal medical treatment before vs after surgery • Hormonal medical treatment before and after surgery vs no treatment/usual care **For non-pharmacological management specific to pain:** • Non-pharmacological management vs no treatment, usual care or placebo • Non-pharmacological management A vs non-pharmacological management B • Non-pharmacological management vs pharmacological treatment (hormonal medical treatment, analgesics and neuromodulators) • Non-pharmacological management vs surgical interventions **For NMA outcomes**: • All interventions specified in this protocol

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Item	Details
Outcomes	• Pain relief • Health related Quality of Life • Rate of success (Disease recurrence and subsequent reoperation rate) • Adverse events (specifically withdrawal due to adverse events) • Surgical complications • Participant satisfaction with treatment • Effect on daily activities (measured as proportion of women who reported activity restriction which could include; absence from work and school) Additional outcomes for non-pharmacological treatments: • Reduction in size and extent of endometrial cysts • Adherence to treatment programme
Importance of outcomes	Preliminary classification of the outcomes for decision making: Critical: • Pain relief • Health related Quality of Life • Adverse events (specifically withdrawal due to adverse events) • Adherence to treatment programme (for non-pharmacological treatments) Important: • Rate of success (Disease recurrence and subsequent reoperation rate) • Participant satisfaction with treatment • Effect on daily activities (measured as proportion of women who reported activity restriction which could include; absence from work and school) • Reduction in size and extent of endometrial cysts (for non-pharmacological treatments)
Setting	No particular setting specified
Stratified, subgroup and adjusted analyses	The following groups of interventions will be reviewed, analysed and presented separately. However, for NMA outcomes, interventions will be included in the same network provided study populations are considered to be sufficiently similar: • Hormonal medical treatments • Surgical interventions • Combinations of treatments (hormonal medical treatment before or after surgery compared to surgery alone) • Non-pharmacological management specific to pain Pre-specified subgroup analyses: • Type of diagnosis of endometriosis • Types of pain ○ cyclical vs non-cyclical ○ period-like, sharp, dyschezia, painful intercourse, chronic pelvic pain • Site of endometriosis (not specified, ovarian, superficial and deep infiltrating {bladder, peritoneal, recto vaginal}) • Bowel involvement (shave/skinning, disk, bowel resection) • Route of administration
Language	English
Study design	• Systematic reviews of RCTs • RCTs • In absence of full text published RCTs, conference abstracts will be considered.

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Item	Details
	• Cross over RCTs will be considered where it is appropriate • Studies with >66% women with endometriosis will be included. If the analysis has been performed for the women with endometriosis separately then only this data will be extracted. • RCTs with <10 participants in each arm will not be included
Search strategy	See appendix for full strategies
Review strategy	**Appraisal of methodological quality:** • The methodological quality of each study should be assessed using quality checklists and the quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** • Network meta-analysis will be conducted where data are available for the following outcomes (see NMA protocol): ○ Pain relief (Biberoglu and Behrman scale, Visual Analogue Scale) ○ Withdrawal due to adverse events ○ Quality of life (SF-36 scale) • Pairwise meta-analysis will be conducted where appropriate for all other outcomes • Default MIDs will be used: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes to assess imprecision. • For Visual Analogue Scale (VAS) outcomes related to pain an MID of 1 cm (for a 10cm scale) will be used (Gerlinger 2010). • When meta-analysing continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed. • If studies only report p-values, this information (including the sample size) will be provided in GRADE tables with a note that imprecision could not be assessed
Equalities	None noted

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