D.9 Pharmacological management – Neuromodulators

Item	Details
Area of the scope	Pharmacological and surgical treatments including analgesics, hormonal medical treatments, neuromodulators, ablation, excision and hysterectomy with or without oophorectomy
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?
Review question	What is the effectiveness of neuromodulators for treating endometriosis, including recurrent and asymptomatic endometriosis?
Objective	The aim of this review is to determine the effectiveness of neuromodulators for treating endometriosis, including recurrent and asymptomatic endometriosis.
Population and directness	• Women with endometriosis of any stage or severity. These may also include suspected diagnoses Exclusions: • Studies with indirect populations (such as women with dysmenorrhea, women with non-confirmed pelvic pain, or post-menopausal women) • 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. • mixed populations of women with pelvic pain where less than 66% of women have a diagnosis of endometriosis
Intervention	Neuromodulators (neuropathic analgesia) of any type and administered at any dose, frequency, treatment duration, or by any type of administration: • Tricyclics; Amitriptyline Nortriptyline, • Serotonin–norepinephrine reuptake inhibitors (SNRIs); Duloxetine, Mirtazapine, Venlafaxine • Local anaesthetics: lidocaine (topical and infusion) • Capsaicin patches • NMDA antagonist: Ketamine • Anticonvulsants: Gabapentin, Pregabalin, Tiagabine, Carbamazepine, Phenytoin, Valproate Topiramate

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Item	Details
	• Nerve blocks Excluded intervention • Nerve ablation - Laparoscopic uterine nerve ablation (LUNA) is covered by a NICE Interventional Procedure Guideline (IPG) with the following recommendation: *The evidence on laparoscopic uterine nerve ablation (LUNA) for chronic pelvic pain suggests that it is not efficacious and therefore should not be used.*
Comparison	• Neuromodulators vs no treatment / usual care • Neuromodulators vs placebo • Neuromodulators A vs Neuro-modulators B • Neuromodulators vs other pain management drug (see analgesics protocol) • Neuromodulators vs hormonal treatment • Neuromodulators vs surgical treatment
Outcomes	• Pain relief • Health related Quality of Life • Rate of success (Disease recurrence and subsequent reoperation rate) • Pregnancy rate/ fertility • Unintended effects from treatment (side effects and complications) • Participant satisfaction with treatment • Analgesic use Effect on daily activities (measured as proportion of women who reported activity restriction which could include; absence from work and school)
Importance of outcomes	Preliminary classification of the outcomes for decision making: Critical (up to 3 outcomes): • pain relief • health related quality of life • adverse events Important but not critical (up to 3 outcomes): • number of women requiring more surgery • absence from work and other activities of daily living • fertility • analgesic use
Stratified, subgroup and adjusted analyses	Stratification: • Type / class of neuromodulator Subgroups: Population related: • 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}) Treatment related: • Dosage • Route of administration
Language	English
Study design	Systematic reviews of RCTs RCTs

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Item	Details
	Comparative cohort studies In the absence of full text published RCTs, conference abstracts are being considered. Cross over RCTs will be considered where it is appropriate RCTs with <10 participants in each group and observational studies with <30 participants will not be considered
Setting	No particular setting specified.
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Limit to English language and human-only studies where appropriate Supplementary search techniques: No supplementary search techniques will be used. See appendix for full strategies
Review strategy	Appraisal of methodological quality: The methodological quality of each study should be assessed using quality checklists (eg AMSTAR for systematic reviews, Cochrane RoB tool for RCTs, CASP for cohort studies) and the quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Meta-analysis will be conducted where appropriate. Default MIDs will be used: 0.8 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	Adolescents are noted as a secific subgroup requiring consideration in the equalities impact assessment
Notes/additional information	

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