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Systematic Review

Effectiveness and Safety of Emerging Therapies Versus Conventional Treatments or Placebo for Chronic Gynecologic Pelvic Pain in Adult Women: A Systematic Review

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Abstract

Background: Chronic gynecologic pelvic pain (CGPP) is a multifactorial condition associated with functional impairment and heterogeneous treatment responses. Emerging therapies are increasingly being used. However, their comparative effectiveness and safety remain uncertain. **Methods:** We conducted a systematic review of comparative studies in adult women (≥18 years) with CGPP lasting ≥6 months. Interventions included pelvic floor rehabilitation, botulinum toxin type A (BoNT-A), psychological and behavioral therapies, nutraceuticals, and oral gonadotropin-releasing hormone (GnRH) antagonists. MEDLINE, EMBASE, and CENTRAL were searched from inception without language restrictions. Study selection and data extraction were performed independently by two reviewers. Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. Due to substantial heterogeneity across study populations, interventions, comparators, outcomes, and follow-up durations, a meta-analysis was not performed. Findings were synthesized narratively and stratified according to predefined pain phenotypes based on the primary clinical diagnosis reported in each study, including endometriosis-associated pain, pelvic floor myofascial pain, and vulvodynia. Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. **Results:** 21 studies were included. Pelvic floor training was associated with modest reductions in current pelvic pain at 4 and 12 months. Evidence for BoNT-A was inconsistent across studies of pelvic floor myalgia and vestibulodynia. Psychological interventions demonstrated more consistent improvements in functional and psychosocial outcomes than in pain intensity. GnRH antagonists produced dose-dependent reductions in endometriosis-associated pain, with higher responder rates than placebo, but were associated with hypoestrogenic adverse effects. **Conclusions:** Emerging therapies may offer benefits in specific CGPP phenotypes; however, the available evidence remains heterogeneous. A phenotype-informed, multimodal treatment approach may be considered, with careful attention to potential safety trade-offs. **Registration:** This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261302453. Registration record: https://www.crd.york.ac.uk/PROSPERO/view/CRD420261302453.

Keywords: chronic pelvic pain; endometriosis; pelvic floor disorders; gonadotropin-releasing hormone antagonists; cognitive behavioral therapy

1. Introduction

Chronic gynecologic pelvic pain (CGPP) affects a substantial proportion of women of reproductive age and represents a significant clinical and public health burden due to its impact on quality of life, functional status, and healthcare utilization [1]. Current management strategies encompass hormonal suppression, surgical intervention, analgesics, and multidisciplinary approaches [2]. Although these interventions may provide benefit for some patients, many women continue to experience persistent symptoms or treatment-related adverse effects. Consequently, there has been growing interest in therapies targeting distinct components of the pain pathway.

The pathophysiology of CGPP is complex, involving interactions among peripheral drivers, including endometriotic lesions and pelvic floor dysfunction, central sensitization processes, as well as psychosocial factors that modulate pain perception and disability [3]. Importantly, multiple pelvic pain syndromes frequently coexist, including neuropathic conditions such as pudendal neuralgia, which may influence symptom presentation and treatment response. CGPP encompasses a spectrum of overlapping conditions, including endometriosis-associated pain, pelvic floor myofascial pain, and vulvodynia, with contributions from nociceptive, neuropathic, and nociplastic mechanisms [3,4].

Botulinum toxin type A (BoNT-A) has been evaluated for pelvic floor hypertonicity, although results remain inconsistent [3,4,5]. Pelvic floor rehabilitation is included as part of multidisciplinary management approaches for chronic pelvic pain [6,7]. Psychological and behavioral interventions aim to address central pain processing and coping strategies, which are increasingly recognized as key contributors to chronic pain states [8]. Additionally, oral gonadotropin-releasing hormone (GnRH) antagonists have emerged as pharmacological options for endometriosis-associated pain [9]. Multimodal physical therapy has also been evaluated as a treatment option for provoked vestibulodynia [10].

Consensus classification frameworks have also standardized the terminology for persistent vulvar pain and vulvodynia [11], while clinical guidelines have provided recommendations for the management of endometriosis [12]. Longer-term evidence has further evaluated the efficacy and safety of relugolix combination therapy for endometriosis-associated pain [13].

Despite increasing clinical use, the evidence base for these interventions remains heterogeneous and fragmented. Differences in pain phenotypes, intervention protocols, outcome measures, and study designs complicate interpretation and limit the ability to draw definitive conclusions. Therefore, a structured synthesis stratified by pain phenotype and intervention class is warranted.

The objective of this systematic review was to evaluate the effectiveness and safety of emerging therapies for CGPP in adult women, with a focus on phenotype-specific outcomes and variability in treatment response.

2. Methods

2.1 Study Design and Eligibility

We conducted a systematic review of comparative clinical studies, prioritizing RCTs. Eligible studies included adult women aged 18 years or older with a diagnosis of CGPP of at least six months. Inclusion criteria were as follows: endometriosis-associated pain, pelvic floor myofascial pain, and vulvodynia. Exclusion criteria were as follows: acute pain, malignancy, pregnancy-related conditions, or non-gynecologic pain syndromes.

2.2 Interventions and Comparators

Interventions of interest included pelvic floor physical therapy, BoNT-A injections, psychological and behavioral therapies, nutraceutical interventions, and oral GnRH antagonists. Comparators comprised placebo, usual care, wait-list controls, or active treatments. Given the distinct pathophysiology underlying endometriosis, studies evaluating GnRH antagonists were analyzed as a separate subgroup and interpreted independently from those addressing other CGPP phenotypes.

2.3 Outcomes

Primary outcomes included pain intensity and safety parameters, such as adverse events and treatment discontinuation rates. Secondary outcomes included quality of life, functional status, psychological outcomes, and global improvement. Safety data were evaluated across all included studies. Reported adverse events and other treatment-related safety outcomes were summarized when available, while studies with absent or insufficient safety reporting were explicitly identified.

2.4 Search Strategy and Study Selection

MEDLINE, EMBASE, and CENTRAL were searched from inception without language restrictions. Two reviewers independently screened titles and abstracts and performed full-text review and data extraction. Disagreements were resolved through discussion or, when consensus could not be reached, by adjudication from a third reviewer. Study selection was documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1).

2.5 Risk of Bias and Certainty of Evidence

Risk of bias was assessed using the RoB 2 tool for randomized controlled trials. Certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, considering risk of bias, inconsistency, indirectness, and imprecision.

2.6 Data Synthesis

A meta-analysis was not performed due to substantial clinical and methodological heterogeneity, including differences in pain phenotypes, intervention characteristics, comparator types, outcome measures, and follow-up durations. Therefore, a structured narrative synthesis was conducted, stratified by pain phenotype and intervention class. Pain phenotypes were categorized a priori based on the primary clinical condition reported in each study, including endometriosis-associated pain, pelvic floor myofascial pain, and vulvodynia.

3. Results

3.1 Study Characteristics

Included studies evaluated emerging interventions across heterogeneous CGPP phenotypes (Table 1, Ref. [14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34]), encompassing endometriosis-associated pain [14,27,31], pelvic floor myofascial pain [16,17], and provoked vestibulodynia [15]. The distribution of interventions varied across phenotypes. Pelvic floor–directed interventions were primarily assessed in populations with endometriosis and pelvic floor myalgia, whereas BoNT-A studies focused on vestibulodynia and pelvic floor dysfunction. Psychological and behavioral interventions were

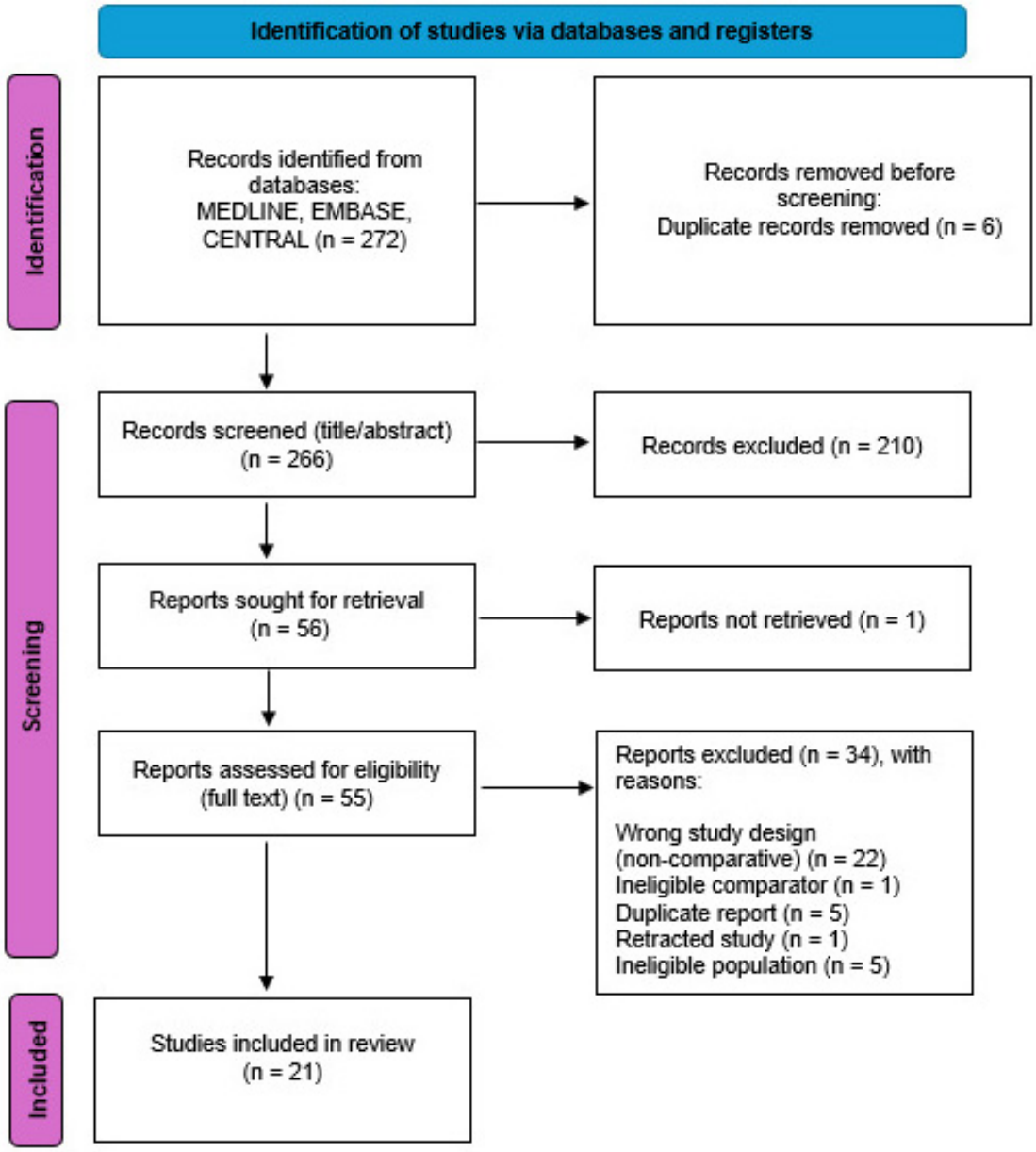

Fig. 1. PRISMA 2020 flow diagram of study selection.

evaluated predominantly in endometriosis-associated pain cohorts, often within broader multidisciplinary treatment frameworks.

Interventions included pelvic floor training [14], botulinum toxin injections [15,16,17], nutraceutical adjuncts [18], psychological and behavioral therapies [19,20,21,22], and oral GnRH antagonists, such as elagolix, linzagolix, relugolix, and ASP1707 [23,24,25,26,27,28,29,30,31,32,33,34]. GnRH antagonist trials were conducted exclusively in endometriosis cohorts and were generally larger and more standardized in design than trials evaluating other intervention classes.

3.2 Efficacy

Pain outcomes are summarized in Table 2 (Ref. [14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34]) and are presented by intervention class and underlying pain phenotype. Pelvic floor training was associated with modest reductions in current pelvic pain at 4 and 12 months in women with endometriosis-associated pain [14]. Nonetheless, these effects were not consistently observed across all pain domains.

Botulinum toxin studies reported heterogeneous findings across populations with pelvic floor myalgia and vestibulodynia. Several trials demonstrated short-term improvements in pain-related outcomes; however, between-group differences were inconsistent, and results varied according to study design, injection protocols, and outcome measures [15,16,17].

Table 1. Characteristics of included studies.

Intervention	Study	Population	Intervention details	Comparator	Follow-up
PFMT	Gabrielsen et al. (2025) [14]	Women aged 18–45 years with surgically confirmed endometriosis; NRS ≥4	PFMT + supervised exercise + home program	Pain education	4, 12 months
BoNT-A (vestibulodynia)	Diomande et al. (2019) [15]	Provoked vestibulodynia	BoNT-A 50–100 U (subcutaneous)	Placebo	3 months
BoNT-A (PF myalgia)	Dessie et al. (2019) [16]	Chronic pelvic pain with pelvic floor myalgia	BoNT-A + PFPT	Placebo + PFPT	2–12 weeks
BoNT-A (PF spasm)	Abbott et al. (2006) [17]	Chronic pelvic pain >2 years with pelvic floor spasm/myalgia	BoNT-A (80–100 U)	Placebo	3–6 months
Nutraceutical	Cobellis et al. (2011) [18]	Endometriosis (rASRM stage I–II)	PEA + transpolydatin	Placebo or celecoxib	3 months
CBT (online)	Chandra et al. (2026) [19]	Endometriosis-associated chronic pelvic pain	Internet-based CBT	Usual care or wait-list	8–12 weeks
ACT/mindfulness	Hansen et al. (2023) [20]	Endometriosis; NRS ≥5	ACT-based group program	Wait-list	Not reported
Psychotherapy	Beissner et al. (2018) [21]	Laparoscopically confirmed endometriosis	CBT + somatosensory therapy	Wait-list	3 months
CBT (in-person)	Donatti et al. (2025) [22]	Endometriosis; VAS ≥5	Individual CBT	Usual care	4 months
GnRH antagonist	Carr et al. (2013) [23]	Endometriosis	Elagolix 150 mg once daily	Placebo	8 weeks
GnRH antagonist	Diamond et al. (2014) [24]	Endometriosis	Elagolix 150–250 mg once daily	Placebo	12–24 weeks
GnRH antagonist	Carr et al. (2014) [25]	Endometriosis	Elagolix (once or twice daily)	(DMPA-SC)	24 weeks
GnRH antagonist	Taylor et al. (2017) [26]	Endometriosis	Elagolix 150–200 mg	Placebo	3–6 months
GnRH antagonist	Abrao et al. (2021) [27]	Surgically confirmed endometriosis	Elagolix	Placebo	3–6 months
GnRH antagonist	Ács et al. (2015) [28]	Endometriosis	Elagolix	Placebo or leuprorelin	Not reported
GnRH antagonist	Donnez et al. (2020) [29]	Endometriosis-associated pain	Linzagolix 50–200 mg	Placebo	12–24 weeks
GnRH antagonist	Donnez et al. (2024) [30]	Surgically confirmed endometriosis	Linzagolix ± add-back therapy	Placebo	3–6 months
GnRH antagonist	Osuga et al. (2021) [31]	Endometriosis	Relugolix 10–40 mg	Placebo or leuprorelin	12 weeks
GnRH antagonist	Osuga et al. (2021) [32]	Endometriosis (extension study)	Relugolix	Placebo or leuprorelin	24 weeks
GnRH antagonist	Harada et al. (2022) [33]	Endometriosis	Relugolix 40 mg	Leuprorelin	24 weeks
GnRH antagonist	D'Hooghe et al. (2019) [34]	Surgically confirmed endometriosis	ASP1707 3–15 mg	Placebo or leuprorelin	12–24 weeks

PFMT, pelvic floor muscle training; PFPT, pelvic floor physical therapy; BoNT-A, botulinum toxin type A; CBT, cognitive behavioral therapy; ACT, acceptance and commitment therapy; NRS, numeric rating scale; VAS, visual analog scale; rASRM, revised American Society for Reproductive Medicine classification; DMPA-SC, depot medroxyprogesterone acetate (subcutaneous); QD, once daily; GnRH, gonadotropin-releasing hormone; PEA, palmitoylethanolamide; U, units.

Table 2. Efficacy/effectiveness outcomes of included studies.

Intervention	Study	Comparison	Outcomes	Key findings
PFMT	Gabrielsen et al. (2025) [14]	PFMT + exercise vs. education	Pain (NRS), dyspareunia, urinary symptoms	Modest reduction in current pain at 4 and 12 months; no consistent effect on worst pain or dyspareunia
BoNT-A (vestibulodynia)	Diomande et al. (2019) [15]	50–100 U vs. placebo	Pain (VAS), sensitivity, sexual function	No significant between-group differences across outcomes
BoNT-A (PF myalgia)	Dessie et al. (2019) [16]	BoNT-A + PFPT vs. PFPT	Pain, pelvic floor symptoms	No consistent between-group differences in pain; limited improvements in pelvic floor scores
BoNT-A (PF spasm)	Abbott et al. (2006) [17]	BoNT-A vs. placebo	Pain, pelvic pressure, global improvement	Mixed results; some improvements in pelvic pressure and global outcomes
Nutraceutical	Cobellis et al. (2011) [18]	PEA + transpolydatin vs. placebo/active comparator	Pain (VAS), satisfaction	Improvements in pain and satisfaction reported; effects were smaller compared with active comparators
CBT (online)	Chandra et al. (2026) [19]	iCBT vs. usual care	Disability, mood, pain	Improvements in disability and mood; modest and variable effects on pain intensity
ACT/mindfulness	Hansen et al. (2023) [20]	ACT vs. wait-list	Pain, QoL, symptoms	Improvements mainly in quality of life; inconsistent effects on pain
Psychotherapy	Beissner et al. (2018) [21]	Therapy vs. wait-list	Pain, psychological outcomes	Limited between-group differences; small sample size
CBT (in-person)	Donatti et al. (2025) [22]	Individual CBT vs. usual care	Pain perception, coping strategies, depression, stress, QoL	Significant improvements in pain perception, coping, psychological outcomes, and quality of life compared with usual care
GnRH antagonist (elagolix)	Carr et al. (2013) [23]; Diamond et al. (2014) [24]; Carr et al. (2014) [25]; Taylor et al. (2017) [26]; Abrao et al. (2021) [27]; Ács et al. (2015) [28]	Elagolix vs. placebo/active comparator	Dysmenorrhea, nonmenstrual pelvic pain, overall pelvic pain, responder rates	Reductions in endometriosis-associated pain and generally higher responder rates compared with placebo; efficacy findings were broadly consistent across baseline patient subgroups.
GnRH antagonist (linzagolix)	Donnez et al. (2020) [29]; Donnez et al. (2024) [30]	Linzagolix vs. placebo	Dysmenorrhea, nonmenstrual pelvic pain	Dose-dependent improvements in pain outcomes
GnRH antagonist (relugolix)	Osuga et al. (2021) [31]; Osuga et al. (2021) [32]; Harada et al. (2022) [33]	Relugolix vs. placebo/active comparator	Pain, symptom scores	Significant reductions in pain; dose-response relationship observed
GnRH antagonist (ASP1707)	D'Hooghe et al. (2019) [34]	ASP1707 vs. placebo/active comparator	Pain scores	Modest improvements in pain outcomes compared with placebo

PFMT, pelvic floor muscle training; PFPT, pelvic floor physical therapy; BoNT-A, botulinum toxin type A; CBT, cognitive behavioral therapy; iCBT, internet-delivered cognitive behavioral therapy; ACT, acceptance and commitment therapy; QoL, quality of life; NRS, numeric rating scale; VAS, visual analog scale; PEA, palmitoylethanolamide; GnRH, gonadotropin-releasing hormone.

Table 3. Safety outcomes of included studies.

Intervention	Study	Comparison	Outcomes	Key findings
PFMT	Gabrielsen et al. (2025) [14]	PFMT + exercise vs. education	Adverse events	No adverse events or symptom worsening reported
BoNT-A (vestibulodynia)	Diomande et al. (2019) [15]	50–100 U vs. placebo	Adverse events	No serious adverse events; transient post-injection pain was commonly reported
BoNT-A (PF myalgia)	Dessie et al. (2019) [16]	BoNT-A + PFPT vs. PFPT	Adverse events	No significant between-group differences; mild and transient adverse events reported
BoNT-A (PF spasm)	Abbott et al. (2006) [17]	BoNT-A vs. placebo	Adverse events	No clear between-group differences; occasional pelvic and urinary symptoms reported
Nutraceutical	Cobellis et al. (2011) [18]	PEA + transpolydatin vs. placebo/active comparator	Adverse events	No significant adverse events or laboratory abnormalities reported
CBT (online)	Chandra et al. (2026) [19]	iCBT vs. usual care	Adverse events	Adverse events were not systematically reported
ACT/mindfulness	Hansen et al. (2023) [20]	ACT vs. wait-list	Adverse events	Safety outcomes not reported
Psychotherapy	Beissner et al. (2018) [21]	Therapy vs. wait-list	Adverse events	Safety outcomes not reported
GnRH antagonist (elagolix)	Diamond et al. (2014) [24]; Carr et al. (2014) [25]; Taylor et al. (2017) [26]; Ács et al. (2015) [28]	Elagolix vs. placebo/active comparator	TEAEs, BMD	Dose-dependent reductions in bone mineral density; increased vasomotor symptoms; other adverse events generally similar across groups
GnRH antagonist (linzagolix)	Donnez et al. (2020) [29]; Donnez et al. (2024) [30]	Linzagolix vs. placebo	TEAEs, BMD	Increased adverse events with higher doses; bone density changes and vasomotor symptoms reported; serious events uncommon
GnRH antagonist (relugolix)	Osuga et al. (2021) [31]; Osuga et al. (2021) [32]; Harada et al. (2022) [33]	Relugolix vs. placebo/active comparator	TEAEs, BMD	Higher frequency of adverse events with increasing dose; common events included vasomotor and menstrual symptoms; reductions in BMD observed
GnRH antagonist (ASP1707)	D'Hooghe et al. (2019) [34]	ASP1707 vs. placebo/active comparator	TEAEs	Adverse events were generally mild to moderate; no major safety concerns were identified

BoNT-A, botulinum toxin type A; PFMT, pelvic floor muscle training; BMD, bone mineral density; TEAEs, treatment-emergent adverse events.

GnRH antagonist trials, analyzed as a separate subgroup, demonstrated more consistent findings within endometriosis-associated pain. Across multiple randomized studies, these agents were associated with higher responder rates and greater reductions in dysmenorrhea and nonmenstrual pelvic pain than placebo or active comparators [24,25,26,27,30,31,32,33,34]. These trials generally employed standardized endpoints and consistent outcome definitions.

Psychological and behavioral interventions were associated with improvements in pain-related and psychosocial outcomes, particularly in measures of function, coping, and quality of life. However, effects on pain intensity were more heterogeneous, and substantial variation was observed across studies in outcome measures and follow-up duration [19,20,21,22].

The nutraceutical intervention (palmitoylethanolamide plus transpolydatin) was associated with improvements in pain scores and patient-reported satisfaction compared with placebo or baseline; however, greater effects were observed with active comparators, suggesting a relatively limited comparative benefit.

3.3 Safety

Safety outcomes were available in a subset of included studies, as several trials did not report adverse events or provided insufficient detail for data extraction. Safety findings are summarized in Table 3 (Ref. [14,15,16,17,18,19,20,21,24,25,26,28,29,30,31,32,33,34]). Pelvic floor training was generally well tolerated, and no serious adverse events were reported in the included studies [14]. Similarly, most botulinum toxin studies did not report serious adverse events. Nevertheless, transient post-injection pain and localized discomfort were commonly described [15,16,17]. Occasional reports of urinary or fecal symptoms were observed, although these were not consistently different between groups.

In contrast, GnRH antagonist trials reported a higher frequency of treatment-emergent adverse events. These included vasomotor symptoms, menstrual changes, and reductions in bone mineral density, with some studies also reporting laboratory abnormalities such as alterations in lipid profiles or liver enzyme levels [27,30,31,33]. The frequency and severity of these events appeared to vary according to dose and treatment duration.

Adverse event reporting was limited or inconsistently described in several psychological and behavioral intervention studies, restricting interpretation of their safety profiles. Overall, differences in reporting standards and follow-up duration across studies limit comparability of safety outcomes.

3.4 Risk of Bias

Risk of bias assessments are presented in Table 4 (Ref. [14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34]). Most studies were judged as having some concerns overall, mainly related to missing outcome data and selective reporting.

Several trials showed low risk or some concerns across the randomization and outcome measurement domains [25,31,34], whereas others were rated as high risk due to deviations from intended interventions or limitations in outcome assessment. These methodological limitations, together with inconsistency and imprecision across studies, contributed to low-to-moderate certainty of evidence.

4. Discussion

This systematic review provides a structured synthesis of emerging therapies for CGPP, highlighting variability in reported outcomes across pain phenotypes and intervention classes. The findings reflect the complexity of CGPP as a heterogeneous clinical entity, in which treatment response may vary according to underlying mechanisms, patient characteristics, and intervention design.

Among the included interventions, oral GnRH antagonists had the most consistent evidence base, particularly for endometriosis-associated pain. These trials were generally larger and employed more standardized outcome measures, which may contribute to consistency across studies [9,10]. Reported improvements in dysmenorrhea and nonmenstrual pelvic pain align with hormonal modulation of disease activity described in the previous literature. However, these findings should be interpreted in the context of relatively homogeneous study populations and the occurrence of hypoestrogenic adverse effects, including reductions in bone mineral density, which remain relevant in clinical decision-making.

In contrast, the evidence for pelvic floor rehabilitation was more variable. Pelvic floor physical therapy comprises a range of modalities, including relaxation techniques, biofeedback, and strengthening approaches, which are often combined and inconsistently reported across studies. This variability may contribute to the modest and heterogeneous effects observed in pain outcomes. In addition, pelvic floor interventions are frequently delivered as part of multimodal care, limiting the ability to isolate their specific contribution.

The findings for BoNT-A were also inconsistent. Differences in injection protocols, dosing regimens, targeted muscle groups, and patient selection likely contribute to variability across studies. Furthermore, the coexistence of multiple pain mechanisms within CGPP populations may influence treatment response, particularly in studies including mixed phenotypes. Although BoNT-A remains of interest in selected patients with pelvic floor dysfunction, current evidence is insufficient to draw definitive conclusions regarding its comparative effectiveness.

Psychological and behavioral interventions demonstrated a distinct pattern, with more consistent improvements in functional outcomes, coping, and psychological

Table 4. Risk of bias assessment (RoB 2).

Study	Randomization	Deviations	Missing data	Outcome measurement	Selective reporting	Overall
Abbott et al. (2006) [17]	Low	Low	Some concerns	Low	Some concerns	Some concerns
Abrao et al. (2021) [27]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Ács et al. (2015) [28]	Some concerns	Low	Some concerns	Low	High	High
Carr et al. (2013) [23]	Low	Some concerns	High	Low	Some concerns	High
Carr et al. (2014) [25]	Some concerns	Low	High	Low	Some concerns	High
Chandra et al. (2026) [19]	Low	High	Some concerns	High	Some concerns	High
Cobellis et al. (2011) [18]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
D'Hooghe et al. (2019) [34]	Low	Low	Some concerns	Low	Some concerns	Some concerns
Dessie et al. (2019) [16]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Diamond et al. (2014) [24]	Low	Low	Some concerns	Low	Some concerns	Some concerns
Diomande et al. (2019) [15]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Donatti et al. (2025) [22]	High	High	Some concerns	High	High	High
Donnez et al. (2020) [29]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Donnez et al. (2024) [30]	Low	Low	Some concerns	Low	Some concerns	Some concerns
Gabrielsen et al. (2025) [14]	Some concerns	Some concerns	Some concerns	High	High	High
Hansen et al. (2023) [20]	Some concerns	High	High	High	High	High
Harada et al. (2022) [33]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Osuga et al. (2021) [31]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Osuga et al. (2021) [32]	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Beissner et al. (2018) [21]	Some concerns	High	Some concerns	High	Some concerns	High
Taylor et al. (2017) [26]	Low	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns

Low, low risk of bias; High, high risk of bias; Some concerns, some concerns of bias.

distress than in pain intensity. This observation aligns with multidimensional models of chronic pain, in which central processing and psychosocial factors play a key role in shaping the pain experience. The relatively modest changes in pain intensity across these studies may reflect differences in outcome prioritization rather than a lack of clinical benefit.

An important consideration in interpreting these findings is the inherent heterogeneity of CGPP. Chronic pelvic pain encompasses overlapping conditions such as endometriosis, pelvic floor dysfunction, vulvodynia, and neuropathic pain syndromes, which are not always clearly distinguished in clinical trials. In addition, subtypes within these conditions may have distinct mechanisms and treatment responses. Limited phenotypic characterization in the included studies may therefore contribute to outcome variability and restrict the identification of patient subgroups more likely to benefit from specific interventions.

Methodological factors should also be considered. Although all included studies were randomized, several raised concerns related to missing data, deviations from intended interventions, and selective reporting. Sample sizes were often limited outside of GnRH antagonist trials, and follow-up durations varied across studies. Differences in outcome measures and reporting further limited comparability and precluded quantitative synthesis.

Limitations

This review has several limitations, including heterogeneity in study design, variability in outcome measures, limited reporting of safety outcomes, and potential risk of bias in the included trials. These factors may affect the comparability and interpretation of the findings. The certainty of evidence ranged from low to moderate across outcomes, primarily due to inconsistency across studies and imprecision in effect estimates, further limiting confidence in the observed findings.

In this context, a structured narrative synthesis stratified by pain phenotype and intervention class was considered more appropriate than quantitative pooling. This approach enables a more clinically interpretable summary of the evidence while acknowledging heterogeneity.

Overall, the findings support a phenotype-informed, multimodal approach to CGPP management, in which interventions may be selected according to the predominant pain mechanism and patient profile. However, the available evidence remains heterogeneous, warranting cautious interpretation. Future studies incorporating clearer phenotypic definitions, standardized outcome measures, and longer follow-up are needed to improve the understanding of treatment effects in this complex condition.

5. Conclusions

The available evidence suggests that emerging therapies may provide benefits for specific CGPP phenotypes; however, the findings remain heterogeneous and of variable certainty. Pelvic floor rehabilitation and psychological interventions were associated with improvements in functional and psychosocial outcomes, whereas GnRH antagonists demonstrated more consistent effects in

endometriosis-associated pain, along with relevant safety considerations.

These findings support a phenotype-informed, multimodal approach to CGPP management. However, clinical decisions should be individualized, considering potential risks, patient characteristics, and variability in treatment response. Future research incorporating standardized outcomes, longer follow-up, and improved phenotypic characterization is warranted to better define the role of these interventions and to identify subgroups most likely to benefit.

Availability of Data and Materials

The data supporting the conclusions of this review are derived from previously published studies, which are cited in the reference list. No new datasets were generated or analyzed for this study. Therefore, data sharing is not applicable.

Author Contributions

MCPB and JPAG conceived and designed the study. MCPB, LNPG, and JEAM conducted the literature search and study selection. MCPB, LNPG, and CDRP extracted and synthesized the data. JPAG and GITR supervised the study, provided methodological guidance, and contributed to the interpretation of the study findings and their clinical implications. MCPB drafted the initial manuscript. All authors critically revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable. This study is a systematic review of published literature and did not involve direct participation of human subjects or animals.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used an artificial intelligence tool (ChatGPT-4o, OpenAI) to assist with language refinement and editorial clarity. The authors reviewed and edited all content generated by the AI tool and take full responsibility for the integrity, accuracy, and originality of the work.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG50521.

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