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## **Evaluation of effectiveness of pharmacological treatment in pelvic congestion syndrome**

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### **ABSTRACT**

Pelvic congestion syndrome (PCS) is a pain syndrome characterized by positional pelvic pain and is associated with pelvic and vulvar varicosities as well as symptoms of dyspareunia and postcoital pain. Since the etiology of PCS is complex, the treatment should be individualized. Despite both pharmacological and interventional methods being used, there is significant predominance of minimally invasive therapies *e.g.* embolization. The study considers the answer to the question of whether pharmacological therapy is altogether effective. Using a combination of keywords, a PubMed search was performed for the years 1987–2022. The relevant articles were appointed and included in this narrative review. Despite the multitude of alternatives for pharmacological treatment, the systemic side effects of the medications used, as well as the interactions between drugs, affect patients' compliance and persistence. Furthermore, the quality of the currently existing evidence, considering the efficacy of the given substances, is low. Because of the adverse effects and thus the limited drug administration period, there is currently insufficient research on long-term effectiveness of the PCS pharmacological treatment. Therefore, prospective, comparative studies with larger patient population sizes are necessary to provide the possibility of efficient pharmacological therapy.

**Key words:** pelvic congestion; chronic pelvic pain; sclero-embolization; pelvic varices

### **INTRODUCTION**

Pelvic congestion syndrome (PCS) is a pain syndrome characterized by positional pelvic pain and is associated with pelvic and vulvar varicosities as well as symptoms of dyspareunia and postcoital pain [1]. It is believed to be one of the causes of chronic pelvic pain (CPP) described as non-cyclical pain of greater than 6-month duration [1, 2]. Pelvic congestion syndrome is caused likely by failure or lack of the valve system in the periovarian and parametrial veins, which by causing reverse blood flow to the ovarian vessels results in visibly dilated veins and varices, as well as by mechanical vessel compression e.g., by the shifted uterus [2]. It can also be caused by a variety of other factors such as: genetic predisposition, anatomical abnormalities, hormonal factors, damage of the vein's wall and hypertension [3]. Since the term “PCS” does not characterize the full spectrum of the disease and that the International Union of Phlebology recommends using “PVD” — pelvic venous disorder, to describe this condition, the authors have decided to use the latter throughout the text [4].

The initial diagnosis of PVD is based on ultrasound imaging, as it has the advantage of allowing dynamic examination with provocative Valsalva maneuvers. Venography remains the gold standard for the final diagnosis [5, 6]. Nevertheless, computer tomography with contrast is becoming the predominant method for imaging vessels of the minor pelvis in many medical centers; magnetic resonance imaging (MRI) without contrast or with the use of gadolinium is an alternative as well. In certain cases, diagnostic laparoscopy is of great significance, as it enables visualization of the causes of PVD, e.g., foci of endometriosis or adhesions [2].

Since the etiology of PVD is complex, therapy should be individualized based on the severity of pain and the patient's needs. Both pharmacological and interventional methods are used. Options for pharmacological treatment include progestin, medroxyprogesterone, danazol, combined oral hormonal contraceptives, phlebotonics, nonsteroidal anti-inflammatory drugs, psychotropic drugs (gabapentin, amitriptyline), dihydroergotamine, goserelin and gonadotropin-releasing hormone (GnRH) agonists as well as psychotropic drugs e.g., gabapentin, amitriptyline. Patients whose symptoms are not manageable with medical therapy can be considered for ligation, embolization, or sclerotherapy of the ovarian veins. Currently one of the prevailing methods, that provide gratifying results, is embolization [2, 3]. Psychotherapy also plays a role in the treatment of this syndrome [4].

## **Objectives**

The study considers the answer to the question of whether pharmacological therapy for PVD is altogether effective and should be used in a line of treatment.

## MATERIAL AND METHODS

The available PubMed database was searched for articles published in English in the period of 1987-2022, using keywords “pelvic congestion syndrome”, “pharmacological treatment”, “embolization”, “chronic pelvic pain”. The search yielded 793 results, from which 22 met authors’ criteria and were included in the analysis. Studies not available as a full text were excluded from the review. The authors explored data on etiology of PVD, the potential treatment, as well as the possible complications and side effects.

## RESULTS

There are numerous alternatives for pharmacological treatment of PVD. Despite the multitude, available therapies do not seem to produce long term improvement [7]. The systemic side effects of the medications used, as well as the interactions between drugs, commonly affect patients’ both compliance and persistence [3].

In the Table 1 [8–12] the authors gathered the most frequent adverse effects of the medication used in the PVD treatment.

**Table 1.** The most frequent adverse effects of the medication used in the pelvic congestion syndrome (PVD) treatment

MEDICATION		SIDE EFFECTS
Symptomatic pain relief treatment	Gabapentin, Amitriptyline	Cognitive impairment, tolerance, car accidents/falls, abuse, dependence liability [8]
	Nonsteroidal anti-inflammatory drugs	Gastrointestinal disorders, gastrointestinal bleeding, suppression of hematopoiesis and agranulocytosis after long-term use [9]
	Dihydroergotamine	Gastric dyspepsia, headache, dizziness, arrhythmias, induction of angina [9]
Hormonal therapy	Danazol	Weight gain, bloatedness [10]
	Medroxyprogesterone (MPA)	Osteoporosis, weight gain and mood swings [11, 12]
	Gonadotropin-releasing hormone (GnRH) agonists <i>e.g.</i> , goserelin	
	Implanon (3-keto-desogestrel)	Hormonal imbalance, osteoarticular and vascular complications, thrombogenesis, amenorrhea, ovulation suppression [9]
	Combined oral hormonal contraceptives	

Venoactive drugs	Micronized purified flavonoid fraction (MPFF)	Upper abdominal pain, nausea, urticaria, diarrhea, gastralgia, flatulence, pain in the upper abdomen [9]
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Since, generally, the response to one drug alone is not sufficient, polypharmacy seems to be necessary. However, the administration of several medications, from different groups, causes their interactions. The most important interactions have been presented in the Table 2 [13].

**Table 2.** The most important interactions between the medications used in the pelvic congestion syndrome (PVD) treatment [13].

	Gabapentin	Amitriptyline	Dihydroergotamine	Danazol	MPA	Goserelin	Implanon	Combined oral hormonal contraceptives
Gabapentin		Increased side effects	–	–	–	–	–	–
Amitriptyline	Increased side effects		Risk of serotonin syndrome	–	–	Qt interval prolongation	–	TCA toxicity and reduced effects; akathisia
Dihydroergotamine	–	Risk of serotonin syndrome		Increase of the plasma concentrations of ergot derivatives (leading to gangrene and myocardial infarction in severe cases)	–	–	–	–
Danazol	–	–	Increase of the		–	–	–	–

			plasma concentrations of ergot derivatives (leading to gangrene and myocardial infarction in severe cases)					
MPA								Therapeutic duplication
Goserelin		QT interval prolongation						
Implanon								Therapeutic duplication
Combined oral hormonal contraceptives		TCA toxicity and reduced effects; akathisia			Therapeutic duplication		Therapeutic duplication	

MPA — medroxyprogesterone; QT — **full name?**; TCA — **full name?**

## DISCUSSION

As known, various medications, with different action mechanisms and diverse efficacy, are accessible for treatment of PVD. The choice of therapy depends on many aspects. There are multiple studies during which the authors attempted to test the effectiveness of pharmacological therapy of PVD. Past analysis showed the following:

1. Sator-Katzenschlager et al. [14] has shown that PVD may be treated sufficiently, although not completely, with gabapentin and amitriptyline. The research was conducted on 56 women (49 included in the final data analysis) with 24 months follow

up with 300–3600 mg gabapentin and 25–150 mg amitriptyline. A significant reduction in CPP scores was achieved in all patients, however the pain relief was substantially greater in patients receiving gabapentin either alone or in combination with amitriptyline than in patients on amitriptyline alone. Long-term outcome was not reported [14].

Poterucha et al. [15] completed a retrospective review of medical records of 13 patients treated with topical amitriptyline 1–2% and ketamine 0.5%, which has shown reduction in CPP in 85% of the patients. One patient (8%) had complete relief, 6 (46%) had substantial relief, 4 (31%) had some relief, and 2 (15%) had no response. Nonetheless neither the duration of treatment, nor long-term effects were reported [15].

2. There is limited data on effectiveness of intravenous dihydroergotamine (DHE). It has been shown that it may be effective in decreasing the size of parametrial veins and easing the pain. Reginald et al. [16] administered 1 mL of dihydroergotamine or 10 ml of placebo in 12 women with PVD. DHE administration resulted in constriction of the uterine and parametrial veins by 35% and a significant alleviation of pain in 95% of the patients. However, the effect was only sustained for two days after which the pain score between groups did not differ significantly [16]. Stones et al. [17] used 1 ml of DHE in 44 women with PVD and achieved reduction in pelvic veins diameter of 21%. Notwithstanding the results, the pain score was not assessed, and the duration of the treatment effects was not reported [17].
3. The hormonal treatment proves out well as the hormonal imbalance is considered one of the causes of PVD.

Farquhar et al. [18] performed a study on 102 women using 50 mg medroxyprogesterone (MPA), placebo and psychotherapy. The duration of treatment was four months with a nine month follow up period. They reported that MPA in combination with psychotherapy was effective in 73% of PVD patients, however the cessation of pain was also noted in 33% of the women who used placebo. The follow up revealed persistent pain in 50% of female patients who underwent MPA and psychotherapy, and in 47% who used placebo [18].

Medroxyprogesterone has also been shown to be effective, by Cheong et al. [10], as it reduced the pain score in VAS (visual analogue scale) by more than 50% promptly after treatment and maintained the aftereffect up to nine months. The study included

750 women — 406 women in the intervention groups and 344 in the control groups [10].

Soysal et al. [12] demonstrated the assets of 6-month therapy with 30 mg medroxyprogesterone and 3.6 mg goserelin. Medroxyprogesterone and goserelin have been used to suppress ovarian function, which diminishes varices by causing venous contraction. The study was performed on 47 women and was followed by a 12-month observation period. The authors reported reduction of symptoms in 65% of women and emphasized the superiority of goserelin to MPA in improving pelvic pain score. During follow-up, persistence of beneficial effects in all the female patients was reported, however the observation was limited to 12 months, thus long-term effects remain unknown [12].

The study by Shokeir et al. [11] has shown that Implanon (subcutaneous 3-keto-desogestrel) is efficient in alleviating symptoms of PVD. 23 women were included in the study which lasted for 12 months. Reduction of pain from 7.7 to 2.4 was reported in 85% of PVD patients. Long-term effects were not described [11].

4. Micronized purified flavonoid fraction (MPFF) has been shown to reduce the severity of pelvic symptoms. Serfaty D et al. [19] performed a prospective observational study based on 1473 women with PMS with congestive components, administering 1000 mg MPFF per day. The study lasted for three months and the authors reported that symptoms of congestion gradually lessened in terms of both frequency and severity by about 60%. Long-term outcome was not reported [19].

Dissimilarly, in the study by Simsek M et al. [20], that lasted for six months, included 20 women and compared usage of 1000 mg MPFF and placebo, it has been shown that reduction in pain in MPFF group is comparable to placebo group. Long-term outcome was not reported as well [20].

Tsukanov YT et al. [21] performed a study on 24 women, administering 1000 mg MPFF per day for one month. Cessation of pain and reduction in the diameter of the pelvic veins was observed in 75% of patients. Nevertheless, there was no follow-up period and long-term outcome remained unknown [21].

Gavrilov et al. [22] demonstrated that MPFF reduced the PVD symptoms, such as pain, heaviness and labia majora swelling, in all the observed patients. Women were administered 1000 mg once daily for two months (35 patients) or 1000 mg twice daily for one month followed by 1000 mg once daily for one month (30 patients) based on



the intensity of pain. Both groups of patients reported reduction in pain severity. A considerable increase in linear blood flow velocity of internal iliac veins was also confirmed in phlebography (10–35%) [22]. Furthermore, it has been demonstrated, also by Gavrilov et al., that a double dose of MPFF (1000 mg twice a day) in the first month of treatment contributed to quicker symptoms decrease. The authors analyzed the efficacy of treatment in 125 women with PVD, administering 1000 mg MPFF once per day for two months in the first group of 65 patients and 1000 mg MPFF twice per day for one month followed by 1000 mg once daily for another month in the second group of 60 patients. The treatment was effective after 13.7 days in the first group and 3.1 days in the second one and the reduction in symptoms was significantly greater in the second group compared to the first group in the second month (46.6% vs 25%) [23].

Although pharmacological methods are- according to the aforementioned studies- effective, their systemic side effects, as well as the interactions between each other resulting from polypharmacy, commonly affect compliance and long-term acceptance. Due to the limited drug administration period, there is currently insufficient research on long-term effectiveness of the PVD pharmacological treatment. Furthermore, the quality of the currently existing evidence, considering the efficacy of the given substances, is low, as the majority of the studies was performed for an insufficient period of time, on groups of patients too small to draw more specific conclusions [10]. Moreover, no sufficient data is available on long-term consequences after suspension of treatment [3]. Therefore, prospective, comparative studies with larger patient population sizes are necessary to provide the possibility of efficient pharmacological therapy.

## **CONCLUSIONS**

As a result of the complexity of PVD's etiology, therapy should be individualized based on the severity of pain and the needs of the particular patients. Both pharmacological and interventional methods can and should be used. Despite the lack of studies considering long-term effectiveness of pharmacotherapy and existence of various adverse effects, the authors believe that it should be used as the first line of PVD treatment and in the transitional period before embolization, as in some of the patients it allowed to achieve a significant improvement. Moreover, it cannot be forgotten that psychotherapy also plays an important role in the treatment of this syndrome [4]. In order not to waste resources or precious time,

patients whose symptoms are not manageable with medical therapy can then be considered for surgical interventions. Pharmacotherapy should not be completely omitted in the treatment of PVD.

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#### ***Conflict of interest***

All authors declare no conflict of interest.

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