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Efficacy of adjunct therapy with citalopram to improve health-related quality of life and associated symptoms in patients with endometriosis: A randomized clinical trial

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ABSTRACT

Aims and Objectives: Given the impact of SSRIs on chronic pain and inflammation in endometriosis pathogenesis, the hypothesis is that incorporating an SSRI drug into the treatment of women with endometriosis may result in a reduction in inflammation and pain. This study aimed to integrate Citalopram into the treatment of endometriosis patients to assess the effects of these medications on endometriosis symptoms and overall health-related quality of life.

Materials and Methods: The first group received a dose of citalopram (20 mg to 40 mg) alongside Verogest 2 mg daily for three months. The placebo group received only a daily dosage of 2 mg Verogest. Medications were administered for 12 weeks. Pelvic pain, dysmenorrhea, and dyspareunia, were assessed using a visual pain ruler and the ENDOPAIN-4D questionnaire before and after the intervention. Additionally, participants completed the EHP30 for Health-related quality of life evaluation. The final analysis compared changes in pelvic pain and health-related quality of life scores between the two groups.

Results: In total, 40 patients were included in both the control and intervention groups, with no discernible differences regarding basic characteristics. Analysis of the EHP-30 questionnaire revealed significant differences between the placebo and intervention groups in control and powerlessness (p=0.013), emotional well-being (p=0.001), and social support (p=0.005). The VAS test demonstrated significant differences in dysmenorrhea (p=0.006), dyschezia (p=0.040), and chronic pelvic pain (p=0.004), while dyspareunia (p=0.081) did not exhibit a significant difference. Evaluation of the ENDOPAIN-4D questionnaire indicated significant improvement in all domains for the intervention group, except for pain-related disability (p=0.117). Moreover, the total score difference was significantly higher (p=0.002) in the intervention group.

Conclusion: In summary, our study indicated citalopram therapy results in a significant decrease in overall pain and associated outcomes, along with a notable improvement in the health-related quality of life compared to the placebo group. Future research should focus on determining the optimal dosage of citalopram and comparing its effectiveness with other SSRIs.

Keywords: endometriosis, ssris, ehp-30, endopain-4d, pelvic pain

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INTRODUCTION

Endometriosis is a prevalent disorder affecting 5% to 10% of reproductive-aged women, characterized by the presence of tissue resembling endometrial stroma and glands outside the uterus. This chronic, estrogen-dependent inflammatory condition leads to various symptoms. In infertile women, the prevalence is 20%-50%, and for those experiencing pelvic pain, it ranges from 20%-70% [1-3]. Factors associated with an elevated risk of endometriosis include nulliparity, prolonged estrogen exposure, early or late menarche, shorter menstrual cycles, heavy menarche bleeding, menstrual outlet obstruction, in utero exposure to Diethylbestrol, height over 68 inches, low body mass index, and a history of physical or sexual abuse during childhood or adolescence, along with a high intake of unsaturated fat. Clinical symptoms encompass chronic pelvic pain, worsening pain during menstruation, painful intercourse, painful bowel movements, and urinary and digestive symptoms, potentially leading to reduced fertility or infertility. These symptoms significantly impact the health-related quality of life and may contribute to psychiatric disorders [4, 5].

The etiology of endometriosis remains unclear, with proposed theories including retrograde flow of endometrial tissue, coelomic metaplasia, stem cell migration, and environmental toxins. Genetic, immunological, and inflammatory factors are believed to be involved in pathogenesis, with chronic pelvic inflammation playing a crucial role [6-8]. The pain associated with endometriosis is not necessarily correlated with the disease stage but is attributed to local inflammation caused by endometriotic lesions. The persistence of chronic inflammation induces chronic stress, potentially explaining various symptoms reported by patients, such as chronic fatigue syndrome, hyperalgesia, and psychiatric disorders related to low serotonin levels. The intricate interplay between chronic pelvic pain and mental health in endometriosis patients remains not fully understood. Coexisting psychological disorders and chronic pelvic pain negatively impact the health-related quality of life, with a higher prevalence of depression, anxiety, and sleep disorders compared to the general population [9, 10].

The treatment of endometriosis typically involves a combination of surgical and drug therapies. However, as of now, there is no definitive cure for endometriosis. When choosing a treatment approach, the guiding principle is to opt for the least expensive and least invasive method that is effective with minimal long-term

side effects. Given the extensive symptoms and chronic nature of the disease, a comprehensive approach can be highly beneficial in alleviating symptoms, especially chronic pain [2-7].

Selective Serotonin Reuptake Inhibitors (SSRIs) represent a class of antidepressants widely used worldwide due to their minimal side effects. They are approved for and employed in the treatment of various conditions such as depression, anxiety and panic disorders, obsessive-compulsive disorders, post-traumatic stress disorder, premenstrual syndrome, irritable bowel syndrome, eating disorders, alcohol abuse, and certain personality disorders. While the use of SSRIs for treating chronic pain has been proposed, its efficacy remains uncertain [5-8]. Antidepressants exhibit potential efficacy in managing chronic pelvic pain, either by directly influencing neural pain mechanisms or by alleviating depressive symptoms that can impact the pain experience and coping mechanisms. In terms of the former, research indicates that these medications modulate spinal and neuronal pathways through the activation or inhibition of neurons at peripheral, spinal, and supraspinal levels. The serotonergic pathways and receptor mechanisms, integral to this neuronal network, play a crucial role. Antidepressants likely relieve symptoms through mechanisms such as acetylcholine receptor blockade, serotonin and norepinephrine reuptake inhibition, and histamine H1 receptor blockade [11-15].

Despite the widespread prescription of SSRIs, their mechanism of action is not fully understood. The proposed theories suggest that SSRIs influence neurotransmitters in the brain, induce changes in brain-derived neurotrophic factor expression, affect brain levels of allopregnanolone, and enhance the actions of gamma-aminobutyric acid [10-14]. Moreover, the inflammatory theory of depression posits an increase in serum levels of pro-inflammatory mediators in depressed patients. As inflammation is implicated in acute and some types of chronic pain, SSRIs may play a role in inhibiting inflammatory processes, offering a potential explanation for their therapeutic effect in chronic pain management. However, the precise nature of this mechanism remains unknown. Recent studies in animal models have described analgesic effects for SSRIs [9-11].

Considering the potential mechanisms of SSRI effects on chronic pain and the involvement of inflammation in endometriosis pathogenesis, the hypothesis is that adding an SSRI drug to the treatment of individuals with endometriosis could lead to a greater reduction in inflammation and consequently less pain [1-9]. Although a study with a small sample size of 14 individuals with chronic pelvic pain demonstrated the effectiveness of citalopram in reducing pain, there is a lack of research specifically investigating the effect of SSRIs on pain in individuals with endometriosis. Therefore, this study aims to include Citalopram (from the SSRI family) in the treatment of endometriosis patients undergoing Verogest treatment to examine the impact of these drugs on endometriosis symptoms and overall health-related quality of life.

MATERIALS AND METHODS

Study design and participants

This clinical trial included women diagnosed with endometriosis, specifically targeting those experiencing symptomatic manifestations such as pelvic pain, dysmenorrhea, or dyspareunia. The research sample comprises women with endometriosis who are candidates for drug treatment to alleviate associated symptoms. The inclusion criteria involve endometriosis patients aged 18 years to 45 years who seek drug interventions to mitigate symptoms and are not currently seeking pregnancy. Exclusion criteria encompass conditions such as pregnancy, breastfeeding, clinical examination findings inconsistent with endometriosis, the necessity for surgical endometriosis treatment, drug intolerance, and contraindication for the use of SSRIs.

After obtaining ethical consent from participants, a comprehensive questionnaire covering demographic details, smoking and alcohol habits, fertility and medical history, surgical history, and current illness details (symptoms, disease duration, endometriosis severity) is administered. Height and weight measurements are recorded. Participants are randomly assigned to one of two groups based on a randomization block list. The first group receives citalopram starting at 20 mg, titrated up to 40 mg, alongside daily Verogest 2 mg for three months. The second group receives a daily 2 mg Verogest tablet along with a placebo similar to the first group. Medications are taken daily for 12 weeks, and treatment compliance is monitored through daily pill count. Participants are instructed to note any additional painkillers taken. Pelvic pain levels, including dysmenorrhea, dyspareunia, and chronic pelvic pain, are assessed before and 12 weeks post-intervention using a visual pain ruler and the ENDOPAIN-4D questionnaire. The EHP30 (Endometriosis Health Profile 30) is completed by patients to evaluate the specific health-related quality of life in endometriosis before and after the 12-week intervention. The final analysis will include comparisons of changes in pelvic pain and health-related quality of life scores within each group and between the two groups.

Randomization

The random assignment list of patients is exclusively accessible to the nurse in the laparoscopy clinic. To conceal the random assignment process, the sequence of treatments will be recorded on cards in order. Subsequently, these cards will be inserted into sealed envelopes. Each envelope will bear a randomly generated 10-digit code, devoid of any discernible pattern or structure, serving as the patient's identification number. Only the project methodologist is privy to the corresponding code. When a patient's eligibility is confirmed by the doctor, the clinic nurse furnishes the envelope to the doctor, and the designated treatment is implemented based on the information enclosed in the envelope. The intervention is conducted in a blinded manner.

Data gathering

After obtaining ethical consent from participants, a comprehensive questionnaire covering demographic details, smoking and alcohol habits, fertility and medical history, surgical history, and current illness details (symptoms, disease duration, endometriosis severity) is administered. Height and weight measurements are recorded. Participants are randomly assigned to one of two groups based on a randomization block list. The first group receives citalopram starting at 20 mg, titrated up to 40 mg, alongside daily Verogest 2 mg for three months. The second group receives a daily 2 mg Verogest tablet along with a placebo similar to the first group. Medications are taken daily for 12 weeks, and treatment compliance is monitored through daily pill count. Participants

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The ENDOPAIN-4D questionnaire, designed to assess painful symptoms associated with endometriosis, underwent validation and reliability testing by Paryush Ahmadpour and colleagues. Their examination of the Persian version revealed a Cronbach's alpha coefficient of 0.96 and an Intraclass Correlation Coefficient (ICC) of 0.94 (95% confidence interval: 0.85 to 0.98). The Persian adaptation demonstrated content validity, construct validity, and acceptable reliability for evaluating pelvic pain in Iranian women with endometriosis.

The EHP30 questionnaire, created by the research unit of the Department of Health Services and Gynecology at the University of Oxford in 2001, evaluates the health-related quality of life in patients with endometriosis. Its validity and reliability were assessed in various countries, including the United States, Brazil, and Australia. The questionnaire assigns scores based on a scale where the first option (indicating the worst health status) receives a score of 5, and the last option (indicating the best health status) receives a score of 1. All items carry equal weight, and the questionnaire provides a single score for overall health-related quality of life. Higher scores indicate lower health-related quality of life, with 100 representing the worst level of health-related quality of life. In Iran, the questionnaire has been standardized, demonstrating good validity and reliability, with a calculated Cronbach's alpha coefficient of 0.94.

RESULTS

Overall, we included 40 patients in both control and intervention group. There were no differences among both groups regarding age, BMI, education, marital, status, and other related characteristics of endometriosis such as previous surgery for the treatment of endometriosis, DIE, endometriosis stage, and complications. Further information regarding such characteristics is a summarized in Table 1.

Tab. 1. Comparing related characteristics among control and intervention groups

		Intervention (n=40)	Placebo (n=40)	p-value
Age		38.5 ± 5.35	35.85 ± 6.93	0.059
BMI		28.38 ± 4.01	28.50 ± 4.47	0.895
Duration		4.65 ± 4.17	4.22 ± 3.48	0.629
Parity	0	15, 37.5%	14, 35%	0.275
	1	9, 22.50%	15, 37.50%	
	2	12, 30%	8, 20%	
	3	1, 2.50%	3, 7.50%	
	4	2, 5%	0, 0%	
	5	1, 2.50%	0, 0%	
Miscarriage	No	27, 67.50%	29, 72.50%	0.626
	Yes	13, 32.50%	11, 27.50%	
Previous Pelvic Surgery	No	22, 55%	29, 72.50%	0.104
	Yes	18, 45%	11, 27.50%	
Previous Endometriosis Surgery	No	28, 70%	30, 75%	0.617
	Yes	12, 30%	10, 25%	
Education	<12	22, 55%	25, 62.50%	0.496
	>12	18, 45%	15, 37.50%	
Marital Status	Not Married	6, 15%	8, 20%	0.556
	Married	34, 85%	32, 80%	
Endometriosis Stage	I	0, 0%	0, 0%	0.609
	II	12, 30%	16, 40%	
	III	21, 52.50%	17, 42.50%	
	IV	7, 17.50%	7, 17.50%	
DIE	No	22, 55%	20, 50%	0.654
	Yes	18, 45%	20, 50%	
Complications	No	19, 47.50%	22, 55%	0.502
	Yes	21, 52.50%	18, 45%	

Among the domains of the EHP-30 questionnaire, there was a significant overall difference among the placebo and intervention groups regarding control and powerlessness (p=0.013), emotional well-being (p=0.001), and social support (0.005). Albeit the difference of scores favored the intervention group in the pain scale and self-image domain, however, the difference was not significant among the two groups Table 2.

Tab. 2. Comparing the results of EHP-30, VAS, and ENDOPAIN-4D among the placebo and intervention group

			Intervention (n=40)	Placebo (n=40)	p-value
EHP-30	Pain scale	Before	21.07 ± 12.46	17.32 ± 12.78	0.187
		After	17.72 ± 11.02	14.82 ± 11.69	0.257
		Difference	-3.35 ± 5.74	-2.50 ± 6.25	0.528
	Control and powerlessness	Before	11.55 ± 8.45	10.5 ± 9.19	0.596
		After	9.6 ± 7.72	10.1 ± 8.97	0.79
		Difference	-1.95 ± 3.58	-0.4 ± 1.41	0.013*
	Emotional well-being	Before	13.95 ± 8.68	11.4 ± 7.46	0.163
		After	9.9 ± 6.97	10.4 ± 7.18	0.753
		Difference	-4.05 ± 4.99	-1 ± 2.56	0.001*
	Social support	Before	8.05 ± 5.73	5.85 ± 4.46	0.059
		After	6.6 ± 5.12	5.77 ± 4.38	0.441
		Difference	-1.45 ± 2.80	-0.07 ± 1.18	0.005*
	Self-image	Before	4.2 ± 4.41	3.42 ± 4.11	0.403
		After	3.85 ± 3.95	3.35 ± 4.06	0.578
		Difference	-0.35 ± 1.49	-0.075 ± 0.34	0.26
VAS	Dysmenorrhea	Before	5.5 ± 2.62	5.72 ± 2.40	0.69
		After	4.65 ± 2.70	5.65 ± 2.47	0.088
		Difference	-0.85 ± 1.61	-0.075 ± 0.69	0.006*
	Dyspareunia	Before	3.05 ± 2.96	2.55 ± 2.75	0.436
		After	2.67 ± 2.65	2.57 ± 2.82	0.87
		Difference	-0.37 ± 1.39	0.02 ± 0.35	0.081
	Dyschezia	Before	1.62 ± 2.40	1.95 ± 2.73	0.574
		After	1.05 ± 2.02	1.85 ± 2.68	0.136
		Difference	-0.57 ± 1.10	-0.1 ± 0.92	0.040*
	Chronic pelvic pain	Before	2.92 ± 2.97	2.2 ± 2.54	0.244
		After	2.2 ± 2.53	2.1 ± 2.39	0.856
		Difference	-0.72 ± 1.19	-0.1 ± 0.59	0.004*
ENDOPAIN	Pain-related Disability	Before	38.87 ± 21.43	37.47 ± 21.84	0.773
		After	34.2 ± 18.72	35.2 ± 20.09	0.805
		Difference	-4.67 ± 8.15	-2.2 ± 5.59	0.117
	Dyspareunia	Before	15.95 ± 14.08	14.12 ± 14.83	0.574
		After	13.62 ± 13.13	13.87 ± 15.08	0.937
		Difference	-2.32 ± 5.33	-0.25 ± 1.80	0.022*
	Painful bowel symptoms	Before	8.4 ± 12.31	10.07 ± 11.01	0.523
		After	6.15 ± 9.32	9.65 ± 10.73	0.123
		Difference	-2.25 ± 4.40	-0.42 ± 2.18	0.021*
	Painful urinary Tract symptoms	Before	5.7 ± 7.82	4.57 ± 6.53	0.487
		After	5.2 ± 7.22	4.67 ± 6.45	0.732
		Difference	-0.50 ± 1.45	0.1 ± 1.00	0.034*
	Total score	Before	68.92 ± 39.80	66.25 ± 42.56	0.772
		After	59.17 ± 35.56	63.47 ± 40.99	0.617
		Difference	-9.75 ± 12.79	-2.77 ± 6.17	0.002*

Among the domains of VAS test, there was a significant difference regarding dysmenorrhea (p=0.006), dyschezia (p=0.040), and chronic pelvic pain (p=0.004). Only dyspareunia (p=0.081) did not show a significant difference among the two group.

Among the domains of ENDOPAIN-4D questionnaire, all domains showed significant improvement among the intervention group except pain-related disability (p=0.117). Also, the difference of total score was significantly higher (p=0.002) among the intervention group (-9.75) compared to the placebo group (-2.77).

DISCUSSION

This randomized clinical trial was designed to assess the efficacy of adjunct citalopram therapy among women undergoing endometriosis treatment. Our results indicate that adjunct citalopram therapy can significantly reduce the overall experienced pain and pain-related outcomes. It also significantly increases the health-related quality of life among these patients compared to the placebo group. The difference in scores was significantly higher among the citalopram group compared to the placebo group in almost every domain of the EHP-30, VAS, and ENDOPAIN-4D questionnaires.

Endometriosis is a persistent and progressive condition characterized by the atypical presence of endometrial-like glands and stroma outside the uterus, giving rise to an estrogen-dependent chronic inflammatory response. Typically, the ectopic endometrium is observed in the pelvic peritoneum and organs, including the ovaries, salpinges, cervix and uterus ligaments, and the surrounding pelvic peritoneum, collectively referred to as pelvic endometriosis [9-11]. Additionally, endometriosis can manifest in organs distant from the pelvis, such as the vagina, vulva, cervix, perineum, urinary system, gastrointestinal tract, thoracic cavity (including lungs and pleura), extremities, skin, and Central Nervous System (CNS), constituting what is known as extra-pelvic endometriosis. The term 'extragenital pelvic endometriosis' accurately denotes lesions affecting pelvic organs like the rectum, sigmoid, and urinary bladder. The coexistence of pelvic and extra-pelvic endometriosis defines external endometriosis, which encompasses approximately 90%–95% of cases. In the remaining instances, ectopic endometrium is alternatively situated within the myometrium, leading to internal endometriosis or adenomyosis. Some theories propose that adenomyosis may result from the infiltration of basal endometrium into myometrial dehiscence. This damage is thought to be associated with chronic proliferation and inflammation in the endometrial-subendometrial unit or archimetra, potentially induced by chronic uterine auto-traumatization, ultimately causing Tissue Injury and Repairing (TIAR) [14-18].

Women diagnosed with endometriosis commonly experience pelvic or abdominal pain, occurring in approximately 60% of cases, along with issues related to infertility. Infertility affects around

one-third of women with endometriosis, and conversely, about 40% of women experiencing infertility have been identified with endometriosis [19-21]. While infertility is a prevalent concern, it lacks specificity, making it essential for physicians addressing fertility concerns to consider the possibility of endometriotic lesions. This consideration is particularly important given the suggestive physical examinations, Trans Vaginal Ultrasound (TVS) signs, and established associations between these conditions [22-24].

Pain is a central aspect of various clinical presentations of endometriosis, manifesting in diverse ways depending on lesion locations and timing. Pain symptoms may manifest as dysuria and dyschezia, representing pain associated with endometriotic lesions in the urinary system and intestinal tract, respectively [25-27]. Dysmenorrhea and dyspareunia, common pain manifestations of Deep Infiltrating Endometriosis (DIE), are also noteworthy. In terms of timing, pain initially linked to the menstrual cycle may evolve into non-cyclic pain due to inflammation, the formation of strong visceral adhesions, and heightened neural sensitivity. Beyond six months, this pain can progress to Chronic Pelvic Pain (CPP) [28-30].

Dysmenorrhea refers to pelvic pain linked with menstrual flow, while deep dyspareunia involves pelvic pain during deep sexual penetration. Chronic Pelvic Pain (CPP) stands out as a prominent element in the symptomatology of endometriosis. CPP is characterized by persistent pelvic pain, lasting a minimum of six months below the umbilicus, of such severity that it results in functional impairment or necessitates medical, and often surgical, intervention [31-33]. The presence or absence of an association with menstrual periods varies. While CPP can be indicative of diverse underlying conditions, it frequently presents as a chronic issue influenced by the central nervous system's processing of threat perception, a phenomenon known as "central sensitization." Central sensitization involves the CNS undergoing a process termed 'wind-up,' establishing a prolonged state of heightened responsiveness. This heightened reactivity lowers the pain threshold for all potential causes, perpetuating pain even after the initial injury has potentially healed [3, 16, 34].

The impact of pain is a dynamic experience, characterized by subjective and multifaceted perceptions, requiring a comprehensive understanding of its features in each individual patient. Pain can manifest as a daily occurrence, a monthly event, or infrequently, with variations over time and across different life stages for each patient. Approximately 25% of affected women remain asymptomatic, irrespective of the dimensions of ectopic endometrial tissue. Hurd's concept of "perceived" pain appears to be unrelated to the disease stage, as observed instances include women with mild endometriosis experiencing debilitating painful symptoms and vice versa [35, 36].

This observation implies that various factors, such as personality traits, emotional and affective elements, coping and behavioral strategies, altered stress reactions, attention, and interpretations, as well as beliefs about pain (e.g., duration, controllability, and cause), may influence the perception of pain, affecting its intensity and tolerability. Psychological processes involving emotions, thoughts, and behaviors engage multiple neuronal networks rather than distinct centers, and their interaction with pain processing is intricate. Additionally, these psychophysiological components appear to play a crucial role in the development of central sensitization [35-41]. Numerous studies have demonstrated the link between stress and reduced pain thresholds. Similarly, a history of mood and anxiety spectrum disorders, along with physical and psychological traumas, significantly predicts the development of central sensitization, contributing to the chronicity of pain. It can be suggested that these psychophysiological factors make individuals more susceptible to becoming centrally sensitized following the onset of pain. Endometriosis exerts a profound impact on self-esteem, affective and emotional stability, as well as the social and occupational functioning of affected women, leading to distress and a substantial decline in the health-related quality of life [38, 40].

A consecutive case series focusing on the treatment of chronic pelvic pain included fourteen women subjected to nortriptyline at a dosage of 100 mg per day following a 2-week upward titration. The primary objective was the reduction of pain. In the two-month assessment, six out of the seven women who continued treatment reported being either pain-free or experiencing significant improvement. However, eight women had dropped out of the study, and the research did not provide details on observed side effects [20].

Another randomized controlled trial was conducted to evaluate the effectiveness of sertraline in 23 women experiencing chronic pelvic pain. The participants were randomly assigned to either receive 50 mg of sertraline twice daily or an identical placebo. After 6 weeks, both groups were switched to a single-blind placebo for 2 weeks. Following the washout period, participants initially on placebo were crossed over to sertraline for another 6 weeks, while those initially on sertraline were crossed over to placebo. The primary outcome measure was pelvic pain intensity assessed by a Composite Pain Intensity score. The study had a Jadad quality score of 4 due to the lack of reported random allocation procedures. Sertraline did not show significant improvements in pain compared to placebo, and the authors did not provide information about side effects [25].

Another team conducted a small RCT involving 14 patients with chronic pelvic pain syndrome. Patients were randomly assigned in a double-blind manner to receive either sertraline 50 mg daily or a matched placebo for 13 weeks. After this period, both investigators and patients were unblinded. Subjects initially assigned to receive sertraline had the option to continue for an additional 13 weeks, while those on placebo could cross over to sertraline. Symptom frequency and severity scores were recorded. The study received a Jadad quality score of 2 as it was unblinded, and the authors did not report the random allocation procedure. While there was no statistically significant difference between the two groups, a trend towards sertraline being associated with improved PSF and PSS scores was observed. The authors noted that sertraline was well tolerated, but additional information about side effects was not provided [28].

A more recent study investigated the effectiveness of citalopram in treating chronic pelvic pain through a consecutive case series involving 14 patients. The citalopram dosage administered ranged from 20mg to 60 mg per day. The primary focus was on assessing changes in pain severity, with an additional evaluation of functional disability in response to citalopram. Although there was a noticeable trend towards improvement in pain severity on the McGill Intensity Scale, no statistically significant differences were observed on the pain disability Index. The commonly reported adverse effects included headache, dry mouth, and abdominal pain [6].

CONCLUSIONS

Our findings revealed that the addition of citalopram therapy leads to a notable reduction in overall pain experience and related outcomes. Furthermore, it significantly enhances the health-related quality of life for these patients when compared to the placebo group. The citalopram group exhibited significantly higher scores than the placebo group across nearly every domain of the EHP-30, VAS, and ENDOPAIN-4D questionnaires. Further studies should be conducted regarding the most efficacious dosage of this drug along with its comparison with other drugs from the SSRI family.

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