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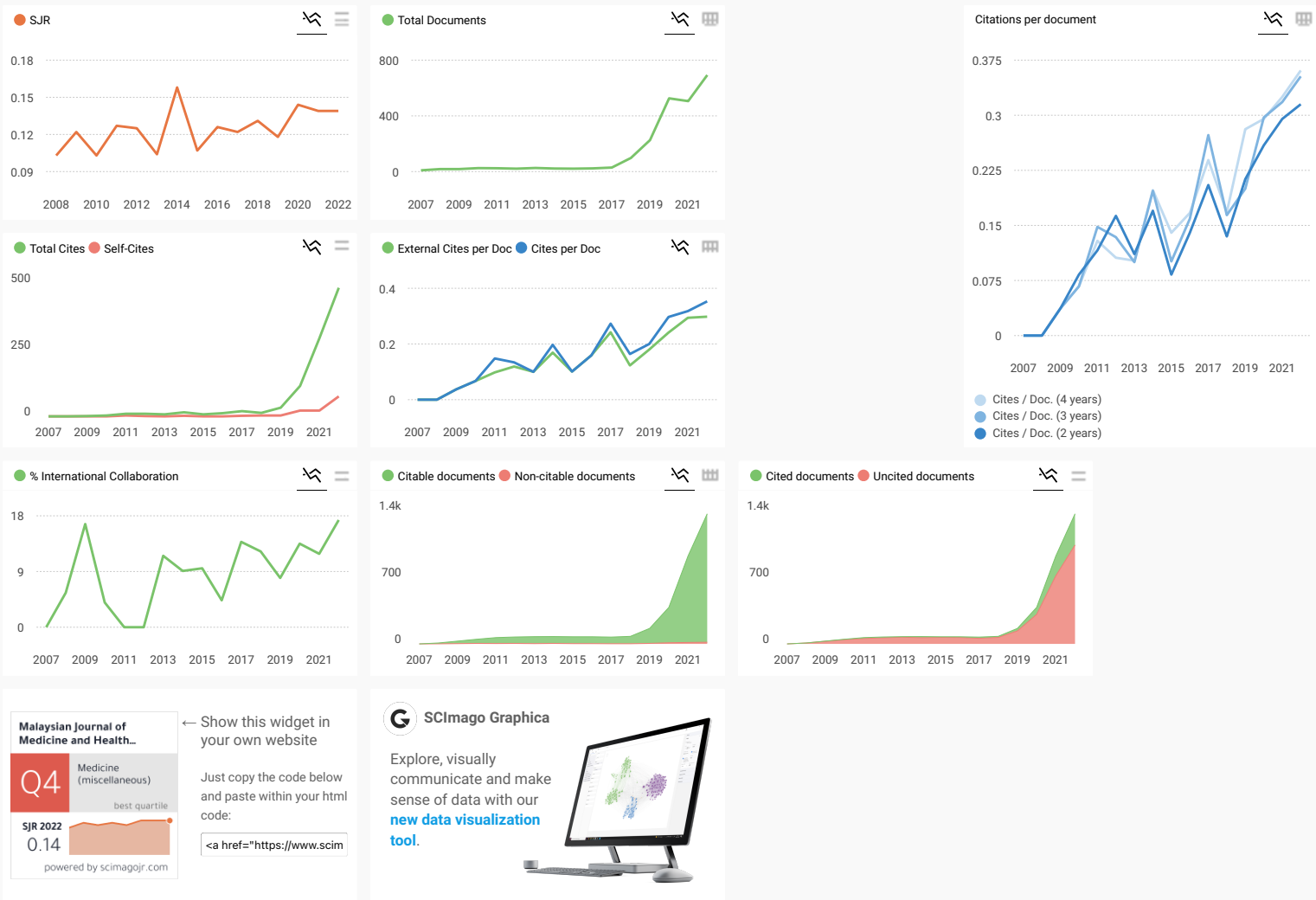
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## REVIEW ARTICLE

# Chronic Pain and Erectile Dysfunction: Mechanism, Treatment, and Future Perspective

I Putu Eka Widyadharma, Eric Hartono Tedyanto, I Made Oka Adnyana, Ida Ayu Sri Wijayanti

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## ABSTRACT

Erectile dysfunction is a problem with multiple causes and is challenging to diagnose. Chronic pain has been associated with erectile dysfunction in some studies. Chronic pain can be a potential direct or indirect cause of sexual dysfunction. A decreased sexual desire due to restricted sexual activity in chronic pain can result in erectile dysfunction. Erectile dysfunction has been linked to migraines, chronic pain, and psychological factors. Multiple neurotransmitters may contribute to the pathophysiology of erectile dysfunction. Depression and anxiety, as well as painkillers like pregabalin and opioids, can be indirect causes of erectile dysfunction. Numerous factors affect the occurrence of erectile dysfunction; therefore, erectile dysfunction must be treated holistically.

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**Keywords:** Chronic Pain, Erectile Dysfunction, Sexual Dysfunction.

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## INTRODUCTION

Erectile dysfunction is a health problem with many contributing factors that reduce the quality of life. According to the Massachusetts Male Aging Study (MMAS), the incidence of erectile dysfunction increases with age, affecting at least 52 percent of men in the United States aged 40 to 70 (1,2). The International Index of Erectile Function (IIEF) questionnaire is a validated tool for determining the severity of erectile dysfunction and the efficacy of therapy (3). The IIEF is a questionnaire with 15 questions; questions 1 to 5 and 15 can be used to classify erectile dysfunction as mild, moderate, or severe (4).

Chronic pain is associated with erectile dysfunction. Chronic pain can be a potential direct or indirect cause of sexual dysfunction (5). Patients with chronic pain have physical and psychological difficulties with sexual interest, sexual activity, and sexual satisfaction (6). Psychological disorders such as depression and anxiety, which frequently occur in patients with chronic pain, can cause an increase in the neurotransmitter noradrenaline, which inhibits an erection (7). Noradrenaline is also involved in pain modulation's intrinsic control. One study indicates an increase in noradrenergic neurotransmission during chronic pain from noradrenergic neurons in the brainstem. This hypothesis strengthens the connection between pain

and erectile dysfunction (8).

## PHYSIOLOGY OF ERECTION

Multiple neurotransmitters contribute to the regulation of erectile function. Dopamine, nitric oxide, glutamate, acetylcholine, oxytocin, and pro-VGF are neurotransmitters that facilitate an erection. Noradrenaline, enkephalin, GABA, and endocannabinoids are inhibitory neurotransmitters of erectile function. These neurotransmitters modulate pain by the gate control theory of the descending analgesic system (9).

Dopamine is the primary neurotransmitter involved in sexual motivation and erection. Dopamine can activate oxytocin neurons by increasing intracellular calcium and nitric oxide levels (10). This will increase cyclic GMP (cGMP), resulting in the relaxation of smooth muscle. Relaxation causes the lacunar cavity in the corpus cavernosum to fill with blood, resulting in compression of the veins, which causes blockage and erection. Erectile dysfunction occurs when there is a disruption in this process (1,11). Note that testosterone is a hormone that can increase dopamine release (12). Neither noradrenergic (anti-erectile) nor nitrenergic (pro-erectile) systems regulate erection. Norepinephrine causes vasoconstriction of blood vessels and smooth muscle contraction of the corpus cavernosum of the penis, which reduces blood flow and inhibits an erection. In the meantime, nitric oxide causes vasodilation of blood vessels and relaxation of the corpus cavernosum smooth muscle, which increases blood flow to the penis, resulting in an erection (13,14).



Noradrenaline is also involved in pain modulation. One study indicates an increase in noradrenergic neurotransmission during chronic pain from noradrenergic neurons in the brainstem. Noradrenaline, enkephalin, GABA, and endocannabinoids, where these neurotransmitters modulate pain in the descending analgesic system according to the gate control theory (8).

## NEUROTRANSMITTERS INVOLVED IN ERECTILE FUNCTION

### 5-hydroxytryptamine (5-HT)

The serotonergic system modulates the sexual processes. Long-term Selective Serotonin Reuptake inhibitors (SSRIs) can result in sexual difficulties, such as ejaculation and erectile dysfunction. The potential underlying mechanism is not entirely understood. It is believed that elevated serotonin levels can interfere with neurotransmitters and hormones like testosterone and dopamine. Testosterone and dopamine are essential to the sexual process. Disturbances in both can cause sexual and erectile dysfunction (15).

### Dopamine

Dopamine is a crucial neurotransmitter in the erectile function process. MPOA, PVN, and accumbens nucleus all contain dopamine. Dopamine can increase intracellular calcium, activating nitric oxide synthase, which activates oxytocinergic neurons and produces nitric oxide. Nitric oxide is a crucial component of the physiological mechanism underlying erection. Inhibition of sympathetic nerve fibers and excitation of parasympathetic nerve fibers results in an erection. The role of dopamine in erectile tissue remains unclear. Dopamine D1 and D2 receptors are suspected to exist in the smooth muscle cells of the corpus cavernosum. Dopamine and dopaminergic neurons trigger an erection by relaxing arterial endothelial cells in erectile tissue (10).

### Glutamate

The anterior cingulate cortex (ACC) of the brain is a cortical region that plays a significant role in the process of sexual arousal. This region's activation correlates with an enhanced sexual urge. According to one study, activation of this cortical region generates an erection. The c-fos gene is a marker for the activation of the ACC region during the process of sexual attraction. The release of the presynaptic neurotransmitter glutamate enhances neuronal activity in this region of the ACC. Glutamate can mediate excitatory transmission in the anterior cingulate cortex (ACC), contributing to sexual activities (16).

### Calcitonin Gene-Related Protein (CGRP)

CGRP is also involved in the physiology of erection. CGRP is present in the sensory artery cavernous nerve fibers, the cavernous artery's walls, and smooth muscle.

It is known that sympathetic nerve fibers express CGRP. In patients with impotence, intravenous injection of CGRP relaxes the corpus cavernosum smooth muscle, increases blood flow, and improves erection (17).

## PATOPHYSIOLOGY OF ERECTILE DYSFUNCTION

Erectile dysfunction is the inability of the penis to maintain an erection for sexual satisfaction. Integration of psychological, neurological, and vascular processes is necessary for erection (18). Several variables can disrupt the normal functioning of an erection. Neurogenic, vascular, organic, and endocrinological issues can contribute to erectile dysfunction. Psychogenic mental disorders, such as depression and anxiety play a crucial role in the development of erectile dysfunction (19). As long as smooth muscle contracts, the penis will remain flaccid; this smooth muscle is controlled by adrenergic (noradrenaline), prostaglandins, endothelin, and intrinsic myogenic control. Non-cholinergic noradrenergic (NANC) nerve fibres secrete nitric oxide in response to sexual stimulation, while cholinergic parasympathetic nerve fibres secrete acetylcholine (ACh). This condition will increase cyclic GMP (cGMP) and decrease intracellular calcium ion levels, resulting in smooth muscle relaxation. Relaxation causes the lacunar cavity in the corpus cavernosum to fill with blood, resulting in compression of the veins, which causes blockage and erection. Erectile dysfunction occurs when this process is disrupted (1,11).

## CHRONIC PAIN AND ERECTILE DYSFUNCTION

We conducted a systematic search on PubMed using keywords "Chronic Pain" and "Erectile Dysfunction" to determine the relationship between chronic pain and erectile dysfunction. The study results and characteristic shown in Table I. These studies were conducted in China, Turkey, India, United States, Taiwan, and Spain. There were four case-control studies, two cross-sectional studies, and one prospective cohort study. The study subjects ranged from 60 to 23,052 samples with a mean age range of 32.26 years to 57 years. The largest sample was done by Huang et al. (20), while the smallest sample was done by Nemichandra et al. (21) Migraine is the most common type of pain in this study.

### Migraine

Erectile dysfunction is associated with migraine and tension-type headaches. Dopamine is fundamental to the pathogenesis of migraines. Dopamine plays a crucial role in regulating erection, and dysregulation of the dopamine pathway negatively affects sexual function. Increased serotonin levels (5-HT) may antagonistically affect testosterone levels in migraine-afflicted male patients, thereby causing sexual dysfunction. In tension-type headaches, recurrent headaches during sexual activity can impair sexual performance. Due to prolonged chronic pain, migraine and tension-type headaches are

**Table 1: Study results**

Author	Main Outcome Measure	Results	Statistical value	Conclusion
Huang et al 2012 (20)	ICD9-CM code 346 HIS IIEF	Patients with a history of migraine were found to have a 1.63 times greater risk of developing erectile dysfunction	OR 1.63 (95% CI, 1.39–1.91) p<0.001	Erectile dysfunction is related to a history of migraines, especially in the younger population.
Aksoy et al 2013 (19)	IHS IIEF	Patients with migraine and tension-type headaches had lower IIEF scores than controls	Mean IIEF scores was 19.83 ± 2.2 in migraines, 20.39 ± 1.35 in tension-type headache patients, and 27.83 ± 0.34 in controls. There were significant differences between tension-type headache and migraine groups and controls (p=0.001)	Other heterogeneous factors contribute to erectile dysfunction in patients with migraines and tension-type headaches.
Deyo et al 2013 (22)	ICD9-CM code 346	People who take opioids have a higher incidence of erectile dysfunction drugs and testosterone therapy  Back pain patients with comorbid depressive disorders independently had a 1.3 times greater risk of experiencing erectile dysfunction	OR 1.45 95% CI 1.12–1.87, P < 0.01  OR 1.30, 95% CI 1.06, 1.60, p=0.01	The dose and duration of opioid therapy are related to the incidence of erectile dysfunction. Depression can be an independent factor in the occurrence of erectile dysfunction.
Bozkurt et al 2014 (23)	IIEF	The use of Pregabalin 300 mg/day for three months in patients with neuropathic pain had a lower mean IIEF-5 value than patients with neuropathic pain without pregabalin and control patients.	IIEF score: 20.87 ± 4.82 in neuropathic pain with pregabalin use (group 1) 25.44 ± 3.23 in neuropathic patients without pregabalin use (group 2) 26.78 ± 3.21 in controls (group 3) (1-2 p=0.000, 1-3 p=0.000, 2-3 p=0.073)	Pregabalin may decrease erectile function in male patients with neuropathic pain
Wu et al 2016 (24)	ICD-9	Migraines are two times more likely to experience erectile dysfunction  Migraines with anxiety have a 3.6 times greater value of experiencing erectile dysfunction than those without anxiety	HR 2.0 95% CI=1.45–2.76 p<0.001  HR 3.6 95% CI, 2.10–6.18). p<0.001	Patients with migraine have a greater risk of developing erectile dysfunction, especially patients with comorbid anxiety
Ajo et al 2020 (25)	MCMI-III VAS-EQ mSLQ-QOL	Chronic pain patients who have comorbid personality disorders, particularly self-defeating dysfunctional (with MCMI-III) associated with severe erectile dysfunction	R=-0.4 (95% CI = -0.605 to -0.145, p = 0.002)	Personality disorders are often found in male chronic non cancer pain patients with erectile dysfunction
Nemichandra et al, 2020 (21)	IHS IIEF MSQoL	Erectile dysfunction was found in 80% of migraine patients (severe headache and disabling), and there was no erectile dysfunction in control patients.	IIEF score 20.00 ± 5.56 in migraine patients 29.17 ± 1.3 in controls (p < 0.001)	Erectile dysfunction is often found in migraine patients. There is a significant negative correlation between erectile dysfunction and severe migraine.

IHS=International Headache Society; IIEF= International Index of Erectile Function Scale; MCMI-III= Millon Clinical Multiaxial Inventory; mSLQ-QOL =Sexual Life Quality Questionnaire; MSQoL=Migraine-Specific Quality of Life Questionnaire; VAS-EQ=Visual Analogue Scale-quality of life;

also associated with depression and other psychiatric disorders. Sexual dysfunction in migraine patients can result in a loss of self-confidence and divorce (27).

Four studies examine the relationship between migraine and erectile dysfunction. According to multiple studies, migraines can be a risk factor for erectile dysfunction. Patients with a history of migraines were 1.63 times more likely to develop erectile dysfunction, according to Huang et al. (OR 1.63, 95% CI 1.39–1.91, p0.001) (29). Aksoy et al. conducted a case-control study on 91 participants (30 migraines, 31 TTH, and 30 controls) (19). It was discovered that the mean IIEF in migraine patients (19.83 + 2.2) and TTH (20.39 + 1.35) was lower than in control patients (27.83 + 0.34). Wu et al. also reported that migraine patients were twice as likely to experience erectile dysfunction (HR 2.0, 95% CI = 1.45–2.76; p0.001) (24). Nemichandra et al. discovered a significant inverse relationship between migraine and erectile dysfunction. There is a significant inverse correlation between migraines and erectile dysfunction; approximately 80% of migraine patients experience erectile dysfunction with a mean IIEF of 20.00 + 5.56

compared to 29.17 + 1.3 in the control group (p 0.001) (21). These findings suggest that migraines and tension-type headaches may contribute to erectile dysfunction.

### Drug-induced

Erectile dysfunction can also occur indirectly in pain patients using anti-pain medications. In one study, patients with the impaired sexual function used antidepressants, anticonvulsants, opioids, and non-opioid painkillers more frequently than those without sexual dysfunction. This indicates a connection between drug use and sexual disorders, including erectile dysfunction (28,29). Pregabalin is a common anticonvulsant treatment for neuropathic pain. According to a study by Mehtap, pregabalin exacerbated erectile dysfunction in male patients with neuropathic pain. Patients with neuropathic pain alone have a lower IIEF score, whereas pregabalin-treated patients have worse outcomes. Pregabalin is an effective analgesic for neuropathic pain, including postherpetic neuralgia, fibromyalgia, radicular pain, cancer, and spinal cord injury (23). Pregabalin induces sexual dysfunction by inhibiting the release of neurotransmitters such as glutamate, substance P, and

calcitonin gene-related peptide (CGRP). Glutamate is a potent neurotransmitter that promotes erections. Substance P is a neurotransmitter involved in sexual behaviour regulation (30). In a study by Bivalacqua et al., CGRP was shown to restore the erectile function of rats with erectile dysfunction. Antimigraine drugs that inhibit CGRP, such as monoclonal antibodies (galcanezumab, eptinezumab), and gepants, increase the risk of erectile dysfunction in migraine patients. If this patient is experiencing impotence for no apparent reason, it is recommended to discontinue these medications while the causes of erectile dysfunction are investigated further (17,31).

Two studies discuss the use of analgesics that can cause impotence. The study by Deyo et al. revealed that opioid users are more likely to take medications for erectile dysfunction (OR 1.45, 95% CI 1.12-1.87, P 0.01), indicating that the dose and duration of opioid therapy are associated with the incidence of erectile dysfunction (22). Bozkurt et al. found that patients with neuropathic pain who took Pregabalin 300 mg/day for three months had a lower mean IIEF-5 (20.87 4.82) than patients with neuropathic pain who did not take Pregabalin (25.44 3.23) and control patients (26.78 4.82) (23).

Opioid use is correlated with hypogonadism. Symptoms of hypogonadism include sexual dysfunction, depression, fatigue, and osteoporosis (22). According to a study by Fraser, hypogonadism was reported in both male and female patients on long-term opioid therapy. However, this study's prevalence, risk factors, and comorbidities were unknown, so the correlation between hypogonadism and sexual dysfunction was weak (32).

### Psychological factors

Erectile dysfunction may result from psychological factors. In a systematic review and meta-analysis, depression and anxiety are the two most prevalent psychological factors. Patients with depression have a propensity for negative thinking and a lack of confidence, leading to a feeling of anxiety that reduces erectile function (33). These patients will experience stress, which will disrupt the Hypothalamic-Pituitary-Adrenal (HPA) axis and cause an increase in catecholamine production, which will relax the cavernosal muscles (28). In patients with anxiety, serotonin (5-HT) levels will increase. Serotonin (5-HT) concentrations will increase in anxious patients. An increase in serotonin will decrease testosterone, which, as stated previously, serotonin is essential for the release of dopamine. As a result, erectile dysfunction and premature ejaculation will result from a testosterone deficiency when dopamine release is reduced (34).

Several studies express psychological factors as well. At least three studies have examined the psychological risk factors leading to erectile dysfunction. Wu et al. explained that comorbid anxiety in patients with migraines increases the risk by 3.6 times (HR 3.6, 95%

CI: 2.10–6.18, P 0.001) (24). According to Deyo et al., back pain patients with the comorbid depressive disorder had a 1.3-fold increased risk of erectile dysfunction (OR 1.30, 95% CI 1.06, 1.60, p=0.01) (22). According to Ajo et al., there is a negative correlation between chronic pain patients with comorbid personality disorders, particularly self-defeating dysfunctional (as measured by the Millon Clinical Multiaxial Inventory-III), and erectile dysfunction ( $R=-0.4$  (95 percent CI = 0.605-0.145, p = 0.002). Personality or psychological disorders are frequently present in male patients with chronic non-cancerous pain (CNCP) and can cause erectile dysfunction (25).

Patients with migraines and tension-type headaches are susceptible to depression and anxiety (35,36). Chronic pain patients are prone to depression and anxiety disorders. In a study of 4557 patients with depressive disorders, Bonierbale et al. discovered that approximately 35% had erectile dysfunction due to endothelial and vascular depression (37). Decreased testosterone levels in older men with erectile dysfunction are associated with depression, which in turn causes erectile dysfunction. Patients with migraines were 3,6 times more likely than the control group to experience erectile dysfunction (who did not experience migraines). Migraine patients with comorbidities like hypertension, dyslipidemia, and anxiety disorders tend to have a higher incidence of erectile dysfunction; therefore, erectile dysfunction must be treated holistically (24).

### TREATMENT

The prevalence of sexual and erectile dysfunction among patients with chronic pain is extremely high. Effective chronic pain management can restore sexual and erectile dysfunction, enhancing the quality of life. Some patients with chronic pain also experience psychological problems. Treating erectile dysfunction in patients with chronic pain that is appropriate for one patient may not be appropriate for others; therefore, the treatment must be individualized. Since there are few specific treatments for erectile dysfunction in patients with chronic pain, it is necessary to comprehend the underlying mechanism of erectile dysfunction in chronic pain. WHOQOL-100 is conducting a study to create a hierarchy of treatment plans and interventions for erectile dysfunction in chronic pain and develop guidelines for managing erectile dysfunction in chronic pain. Several specific treatments for erectile dysfunction are currently available (38).

### Erectile dysfunction in patients with depression

The use of SSRI antidepressants is known to increase serotonin levels, which can lead to erectile dysfunction. Therefore, other antidepressant drugs with fewer side effects, such as bupropion, SNRI, and mirtazapine, should be considered (39). Bupropion and SNRI are alternative antidepressants for erectile dysfunction patients. A study

revealed no significant change in CSFQ values with bupropion ( $p = 0.285$ ). Both bupropion and venlafaxine responded to therapy of  $>50\%$  from baseline, OR 1.93, 95% CI 1.07 – 3.46 for bupropion and OR 1.75, 95% CI 1.04 – 2.85 for venlafaxine (40,41).

Vilazodone and vortioxetine are novel antidepressants that can be used as SSRI replacement therapy. Due to its partial activity at the 5HT<sub>1A</sub> receptor, vilazodone has fewer sexual dysfunction side effects. In placebo-controlled studies, the sexual side effects of vilazodone were minimal. In a 10-week study comparing vilazodone and citalopram, sexual dysfunction side effects, including erectile dysfunction, were more prevalent in the citalopram group, followed by vilazodone and placebo. Vortioxetine is an inhibitor of serotonin reuptake that acts on the 5HT<sub>3</sub> receptor. In seven RCTs, sexual and erectile dysfunction incidence was not significantly different from placebo (42,43).

### Phosphodiesterase 5 Inhibitor (PDE5i)

PDE5i inhibits the hydrolysis of cGMP in the corpus cavernosum by the PDE5 enzyme. Hydrolysis of cGMP can cause constriction of the blood vessels in the corpus cavernosum; therefore, inhibiting hydrolysis can cause vasodilation, resulting in an erection. The PDE5i drugs are sildenafil, tadalafil, and vardenafil. Sildenafil is the first generation of PDE5 used to treat erectile dysfunction. Sildenafil and tadalafil were more effective than placebo in treating erectile dysfunction. PDE5 may be useful for treating erectile dysfunction brought on by SSRI therapy (44-46).

### Saffron

Saffron is a spice derived from the *Crocus sativus* plant. In one study, it was hypothesized that saffron inhibits the reuptake of serotonin and influences nitric oxide levels, thereby playing a crucial role in achieving an erection. Using the IIEF, Modabbernia et al. found that saffron significantly improved erectile function in patients with fluoxetine-induced sexual dysfunction compared to placebo (47,48).

### Apomorphine

Apomorphine is a dopamine receptor agonist that stimulates the D<sub>2</sub>-like receptor on the PVN to produce an erection. Apomorphine's effect on the dopamine D<sub>2</sub> receptor in the spinal cord also contributes to the erection process. According to Matsumoto et al., apomorphine relaxes the erectile tissue, resulting in an erection (10,49).

### Intracavernosal injection (ICI)

In intracavernosal therapy, a vasoactive agent is injected into the corpus cavernosum to relax smooth muscle. The initial injection drug utilized was phentolamine, and the results were favorable. Other drugs, including papaverine, prostaglandins, and vasoactive peptides, have been reported since then. Phentolamine inhibits

postsynaptic alpha-1 adrenergic receptors, thereby preventing corpus cavernosum smooth muscle contraction. Papaverine is an opium alkaloid that acts as a non-specific PDE5i, causing an increase in intracellular cGMP and cAMP and resulting in corpus cavernosum smooth muscle relaxation. Vasoactive intestinal peptide exerts its effect by increasing intracellular cAMP but has no effect on cGMP. VIP is administered in conjunction with phentolamine to treat erectile dysfunction. A combination of ICI and PDE5i is also available. (45,50,51).

### Acupuncture

In western medicine, alternative therapies such as acupuncture are gaining popularity. Acupuncture is an effective treatment for erectile dysfunction. Improvement was observed in 16 male patients with erectile dysfunction who were treated with acupuncture for eight weeks. The mechanism by which acupuncture improves erectile dysfunction is currently unknown. However, it is believed that acupuncture can stimulate nerve endings, thereby altering the levels of norepinephrine, acetylcholine, and other neurotransmitters that play a role in the physiology of erection in the central nervous system (CNS). Guan Yuan (CV4), San Yin Jiao (SP6), Shen Shu (BL23), Zu San Li (ST36), Ming Men (DU4), Tai Chong (LR3), Tai Xi (KI3), and Ci Liao (BL32) are the primary acupuncture points used for the treatment of erectile dysfunction (52,53).

### PAIN CAUSED BY ERECTILE DYSFUNCTION DRUGS

Sildenafil has several side effects, including cluster headaches and migraines. Headache is a side effect that often occurs in patients taking sildenafil 50mg to 150mg. The underlying mechanism is unclear. Some theories declared the inhibitory activity of PDE-6, PDE-5, and PDE-11. PDE-11 inhibition can cause cerebral vasodilation and migraine. Several cases of cluster headaches have been reported from 1999 to 2006. A case of an erectile dysfunction patient who took sildenafil 50 mg for one year was reported. Every 30 minutes after consuming it, the patient experiences cluster headache attacks. Then sildenafil 50mg was replaced with low-dose vardenafil 5mg. 5 days after that, complaints of cluster headaches improved with ED symptoms (55).

The incidence of pain after intracavernous injection is also high. This is because the pain threshold value of each individual is different. In addition, it is also said that pain is related to the type of device used and the dose of drug injected and is very operator-dependent. The most common type of pain experienced by patients after intracavernous injection is an aching and burning sensation (56).

### FUTURE PERSPECTIVE

Several treatments, including genes and stem cells, have been developed for erectile dysfunction. Gene therapy



corrects dysfunctional genes or gene mutations that may cause erectile dysfunction. The intracavernous injection of Maxi-K plasmid DNA improved erectile function as measured by the International Index of Erectile Function (IIEF) after three months of treatment. Stem cells can differentiate into other cell types in response to cell signals. In animal models, bone marrow mononuclear cells (BM-MNC) have been used to treat erectile dysfunction. Yiou et al. administered BM-MNC to male intracavernous smooth muscle following radical prostatectomy. Doppler ultrasound examination revealed an increase in vascularity of the corpus cavernosum and an improvement in IIEF-15 (45,54).

## WHAT WE SHOULD DO

Chronic pain resulting in erectile dysfunction is difficult to diagnose and effectively treat. Numerous factors, including changes in neurotransmitters along the physiological pathway of erection, influence the occurrence of erectile dysfunction in patients with chronic pain. Changes in neurotransmitters may result from the pathophysiological process of chronic pain, psychological factors, and the adverse effects of chronic pain medications. The treatment of erectile dysfunction must be exhaustive and concurrent with the treatment of chronic pain and erectile dysfunction. The importance of educating patients about their condition cannot be overstated. Developing a positive relationship between doctor and patient is also crucial. This is intended to make patients more forthcoming about their conditions, as many cases of erectile dysfunction go undiagnosed due to patients' embarrassment at admitting to having erectile dysfunction. Patients with chronic pain have a decreased quality of life; do not allow erectile dysfunction to make the patient's quality of life worse (45).

## CONCLUSION

According to our review, there is much information regarding the factors related to pain and erectile dysfunction. The most frequent causes of erectile dysfunction in patients with pain are psychological factors such as depression and anxiety. In addition, neurotransmitter disorders can contribute to erectile dysfunction in chronic pain. Improving the patient's quality of life requires a holistic approach to managing patients with chronic pain, including psychological factors and the control of medications. Some drugs may be a benefit in treating erectile dysfunction.

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