Neuroinflammation and Chronic Pelvic Pain Syndrome

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3.1 Chronic Pelvic Pain

Chronic pelvic pain (CPP) is well defined by the European Association of Urology (EAU) as "chronic or persistent pain perceived in structures associated to the pelvis in both men and women. It is frequently correlated with negative behavioral, cognitive, emotional, and sexual effects as well as with suggestive signs of lower urinary tract, bowel, pelvic floor, or gynecological dysfunction. For documented nociceptive pain that becomes chronic/persistent over time, pain must have been permanent or recurrent for at least 6 months. If the sensitization mechanisms of pain are well documented, the pain may be considered chronic, regardless of the time period" [1, 2]. CPP in the female or male genital zone may be localized to the vulva, vagina, or perineum, or may involve intra-abdominal organs, including uterus, ovaries, and fallopian tubes (females), or can involve the prostate, epididymis, scrotum, penis, or testicles (males) [3] (see Table 3.1).

These conditions lead to a substantial burden on limited health care resources. For example, an estimated £158 million are spent every year for the treatment of this disorder in the UK National Health Service [4, 5].

Additionally, in Europe, a study undertaken in 2004 by Breivik and colleagues [6] found that chronic pain of moderate maximum severe intensity occurs in 19% of adult Europeans, extremely disturbing the quality of their lives. There are some changes between states but not much spread is seen.

Considering the complexity of CPP, it is very difficult to treat and these lead to frustration for both patients and their physicians. Treatment should include

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Table 3.1 Classification and actual treatment of CPP in men and women

Urological aspect	Prostate pain syndrome	α-Blockers [152–159] Antibiotic therapy [160–163] Anti-inflammatory drugs [164–167] Opioids [168] 5-α-reductase inhibitors [169–171] Allopurinol [172–174] Phytotherapy [175–177] Pentosan polysulfate [178] Muscle relaxants [155] Pregabalin [179, 180] Botulinum toxin A [181, 182] Physical treatments [183–189] Surgical management [190, 191] Psychological treatment [192, 193]
	Bladder pain syndrome	Analgesics [168] Corticosteroids [194–196] Antiallergics [197–199] Antibiotics [200] Immunosuppressants [201–204] Gabapentin [205, 206] Pregabalin [207] Suplatast tosilate [208] Quercetin [209, 210] Tanezumab [211]
	Genital pain syndrome	Conservative treatment [183, 212–215] Surgery [216] Microsurgical denervation [216–218] Epididymectomy [219–224] Orchiectomy [1, 225] Vasovasostomy [226, 227]
	Urethral pain syndrome	Laser therapy [228] Behavioral therapy [229, 230]
Gynecological aspects	Dysmenorrhea	NSAIDs [231, 232]
	Infection	Treatment of infection depends on the causative organisms such as chlamydia or gonorrhea, or herpes simplex or urinary retention [232–234]
	Endometriosis and Adenomyosis	NSAIDs [231, 232] Laparoscopy [235–237]
	Organ prolapse	Mesh-excisional surgery [238, 239]
	Vaginal and vulvar pain syndromes	Psychological treatment [240–242]
Gastrointestinal aspects	Hemorrhoids	Excisional hemorrhoidectomy [243, 244] Rubber band ligation [243, 244] Hemorrhoidopexy [245]
	Anal fissure	Nitrates and calcium channel blockers [246] Botulinum toxin A injection [247] Sphincterotomy [248]

(continued)

Table 3.1 (continued)

	Proctitis	Antidepressants [249]
	Irritable bowel disease	Fecal microbiota transplantation [250] Dietary modifications [251] Exercise [252–254] Prebiotics and Probiotics [255] Antispasmodic drugs [256, 257] Peppermint oil [256, 258] Antidepressants [259–261] Drugs acting on opioid receptors [262, 263]
Peripherical aspect	Pudendal neuralgia	Conservative management [264, 265] Pudendal nerve block [266, 267] Pudendal nerve decompression [268–270]

multifactorial approaches involving counseling, psychosocial support, medication management, physical therapy, and interventional procedures [1].

3.2 Neuroinflammation

Neuroinflammation is described as an inflammatory reaction inside the spinal cord or brain [7]. Inflammatory events in the peripheral nervous system (PNS) or in the central nervous system (CNS) happen at diverse levels from those of other tissues and involved different types of cells [8, 9]. In particular, the primary distinction relies in the lack of resident dendritic cells in the CNS parenchyma and perivascular macrophages and vascular pericytes take over the functions of mature dendritic cells in the CNS [10]. Secondary, the stimulation of the innate immune cells of CNS parenchyma, such as astrocytes, microglia, and, in some regions, mast cells, may be amplified in clinical conditions such as trauma, stroke, neurodegenerative disease, or growth of a tumor [11–13]. Furthermore, the extravasation of immune cells and molecules towards the inflamed region, indispensable to stimulate complement cascades and maintain the immunity reaction, is crucial for the inflammatory response of the total organism.

However, in the CNS, the blood–CNS barrier limited the permeability of microvessels, making thus the entire inflammatory response incredibly different and difficult. Just stimulated T cells may infiltrate the barrier, but they do not elicit an effective response to inflammation equivalent with that observed in peripheral tissues, where dendritic cells are responsible for the adaptive immune reaction [14]. Due to these features, it is curious to point out that CNS replies to inflammatory events when these exert a direct effect on CNS, for example, in the case of pathogens and tissue injury, and when the inflammatory events are so austere that penetrating T cells are involved. With these clarifications it is crucial to understand the "neuroinflammation" terms that differentiates inflammatory response in the CNS from inflammation reaction in different tissues.

In this view the neuroinflammation terms are a reply of the CNS to altered homeostasis. Principally, one maybe two cell systems are competent to intermediate

this response: glia of the CNS, lymphocytes, macrophages of the hematopoietic system, and monocytes [15]. The actions encouraged by the neuroinflammations are classified as:

- Homeostatic: when it involves different events such as vasodilation or the release of cytokines and neurotrophic factors
- Maladaptive or neurotoxic: when it is characterized by the release of pro-inflammatory factors or the breakdown of blood–CNS barrier
- Anti-inflammatory: when, contrary to what was said above, it involves the release of pro-inflammatory cytokines, neurotrophic factors, neurotransmitters, and cell adhesion molecules

After injury neuroinflammation is dynamically coordinated by a complex network of regulatory mechanisms, which confine the hypothetically damaging effects of persistent inflammation.

In particular, chronic, uncontrolled inflammation is characterized by overexpression of reactive oxygen species (ROS), cytokines, such as TNF-α and IL-1β, and other inflammatory mediators, such as inducible nitric oxide synthase (iNOS).

All these inflammatory molecules are detected following trauma to the CNS, and are involved by employment and trafficking of neutrophils and peripheral macrophages to the injury place. Anyhow, when the inflammatory event is protracted, and the hyperactivation of macrophages is continued, it overpowers the bounds of physiological control and leads to a series of deleterious effects that involve the activation of pro-inflammatory signaling pathways, increase oxidative stress, and death of nearby neurons that provide to the pathogenesis of chronic pain, such as neuropathic pain or neurodegeneration [16, 17].

Last but not least is the role played by neuroinflammation in animal pain models of neuropathic, incisional, inflammatory, and central pain and it is also closely associated with a number of comorbidities of chronic pain such as diabetes, sleep and anxiety disorders, obesity, and depression [18] and for these reasons targeting excessive neuroinflammation can offer new therapeutic approaches for the management of chronic pain and related neurological and psychiatric disorders.

3.3 Microglia and Astrocytes in Chronic Pain

The involvement of microglia and astrocytes in pain processing has been progressively recognized by many laboratories using varied procedures and animal models of temporary or persistent pain. These activations play a crucial role during neuronal recovery after central or peripheral injury [19]. Microglia are macrophage-like cells in the CNS that originate from bone marrow-derived monocytes and that migrate during perinatal development. They are heterogeneously disseminated throughout the CNS. Under physiological situations, microglia are not inactive as many researchers initially assumed, but it has been shown that microglia dynamically sense their environment with their ramified processes [20–22]. In particular, microglia energetically cooperate with synapses to regulate their organizations and

functions in healthy brain [23]. During growth, microglial processes can engulf synapses, and synaptic pruning by microglia, which includes the activation of the complement system, is necessary for normal brain development [24, 25].

During activation, microglia exhibit morphological changes, such as a changing into the amoeboid form, from ramified, to and upregulation of microglial markers such as CCR3/CD11b, major histocompatibility complex II [MHC II], or ionized calcium-binding adaptor molecule-1 [IBA1] [20, 26–28].

Various studies have shown that microglia plays a critical role in neuropathic pain development as well as acute inflammatory pain [29–33]. For instance, it has been shown that minocycline, a nonselective microglia inhibitor, reduces inflammatory or postoperative or neuropathic pain. However, its function in decreasing neuropathic pain in the late phase is restricted [32, 34–36].

Astrocytes are the most abundant cells in the CNS and play several active functions in acute and chronic neurological diseases such as stroke or ischemia [37]. In contrast to microglia and oligodendrocytes, astrocytes formed physically coupled networks intermediated by gap junctions, which, among other roles, simplify intercellular transmission of Ca^{2+} signaling, exchange of cytosolic contents, and display oscillations in ion permeability across astrocytic networks. Gap junction communication is mediated by homo- and heteromeric associations of hemichannels, such as connexin-43 (Cx43), the most prevalent connexin expressed in astrocytes [38]. Although astrocytes are naturally immune labeled by glial fibrillary acidic protein (GFAP).

It is important to note that, every astrocyte forms a nonoverlapping territory or domain, which all together resemble a lattice framework, looking crystalline in nature. On the other hand, the implications of this organization are not fully understood; it becomes lost when astrocytes transition to reactive states [37, 39, 40]. Moreover, astrocytes have wide-ranging interactions with both cerebral blood vessels and synapses, and through these connections they control the increase in blood flow induced by synaptic activity. The astrocyte-mediated blood flow increased is fundamental to the blood-oxygen-level-dependent (BOLD) signal detected by functional magnetic resonance imaging (fMRI) [39]. It is assessed that, in rodents, a single astrocyte can enwrap 140,000 synapses and 4–6 neuronal somata, and can interact to 300–600 neuronal dendrites [40–42]. During synaptic transmission, close contact with neurons and synapses allows astrocytes not only to help and nourish neurons but also to control the external chemical environment. The increasing appreciation for active roles of astrocytes has led to the proposal of a "tripartite synapse" theory, founded on the facts that glia respond to neuronal activity with an increase of their internal Ca^{2+} concentration and cause the release of chemical transmitters from glia themselves, and glial transmitters through a feedback regulation of neuronal activity and synaptic strength [43, 44]. According to this, astrocytic processes are active components of synapses, in addition to pre- and postsynaptic components [45]. On the other hand, active contribution to synaptic activity remains just a possibility because several recent studies have challenged this theory, by demonstrating that alterations in astrocytic Ca^{2+} do not modulate synaptic transmission [46–48].

Due to important modifications in the expression of membrane proteins as well as neural circuits during growth, it is feasible that the notion of receptor-mediated Ca^{2+} signaling will be extended to include other intracellular signaling pathways as a main element defining astrocytic involvement in greater neural function. For example, in the young or adult rodent brain, glutamate-dependent neuroglial Ca^{2+} signaling is different [49–51]. Freshly, it has been demonstrated that receptor-mediated increases in astrocytic Ca^{2+} can control neural network activity by active uptake of extracellular K^+ [52]. Considering that the extracellular concentration of K^+ is an important determinant of the resting membrane potential and thereby of neuronal activity, active uptake of K^+ represents a simple yet powerful tool for rapid variation of neural networks.

Studies using astroglial toxins or astroglial aconitase inhibitor or inhibitors of the astroglial enzyme glutamine synthetase in adult animals suggest that astrocytes play a key role both for the stimulation and preservation of inflammatory and for neuropathic pain [41, 53–60].

Models of neuropathic pain such as rhizotomy and spinal nerve ligation have shown proliferation of spinal cord astrocytes [61, 62]. Conversely, inhibiting astrocyte proliferation in the spinal cord was shown to reduce neuropathic pain [61].

3.4 Molecular Mediators in Chronic Pain

A main problem with regard to glial pain control is understanding how glial mediators are generated and released. In particular, glia produce large molecules such as chemokines, cytokines, proteases, and growth factors, as well as small molecules like glutamate, prostaglandin E2 (PGE2), ATP, and D-serine. These glial mediators can control neuronal and synaptic activity and, most important, pain sensitivity. Among the most well-studied glial mediators are pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β.

These cytokines are upregulated in spinal cord glia after nerve injury, inflammation, and others, and they are involved in the development and maintenance of inflammatory, neuropathic, and cancer pain and morphine tolerance [63–66].

In relation to its well-documented role in modulating peripheral sensitization, TNF-α plays a main role in generating central sensitization and persistent pain [67–73]. IL-1β is induced in astrocytes and microglia after bone cancer, inflammation, and nerve injury [55, 67, 74–78]. It was clearly demonstrated that the inhibition of spinal and brain IL-1β signaling reduces inflammatory, neuropathic, and cancer pain and enhances morphine analgesia [55, 66, 74, 76, 79–81]. Also, chemokines are produced by glial cells, particularly in astrocytes and in neurons [82, 83]. In primary cultures of astrocytes, TNF-α induced rapid expression of (C-C motif) Ligand 2 (CCL2), C-X-C motif chemokine 10 (CXCL10), and C-X-C motif chemokine 1(CXCL1) [84]. Spinal injection of TNF-α-activated astrocytes leads to constant mechanical allodynia through CCL2 release [85]. Additionally, CCL2 expression is further increased in astrocytes of the medullary dorsal horn and contributes to trigeminal neuropathic pain and in spinal nerve ligation induces CCL2

release in spinal astrocytes, and it was observed that intrathecal administration of an MCP-1 neutralizing antibody diminished neuropathic pain [84, 86]. In fact, mice with CCL2 overexpression in astrocytes display pain hypersensitivity [87].

Moreover, growth factors are well known to be induced in spinal glia by nerve injury. In particular, brain-derived neurotrophic factor (BDNF) was upregulated during nerve ligation in spinal microglia, via activation of P2X4 and p38 [88, 89]. Additionally, spinal injection of ATP-activated microglia is sufficient to stimulate mechanical allodynia via releasing BDNF, and, equally, neuropathic pain is repressed by spinal blockade of the BDNF receptor TrkB [30]. Furthermore, treatment of microglial cultures with morphine increases BDNF release, which does not require l-opioid receptor and TLR [90]. BDNF is also induced in dorsal root ganglion (DRG) neurons after nerve injury and can be produced from primary afferents in the spinal cord [91, 92]. Unlike BDNF, basic fibroblast growth factor (bFGF or FGF-2) is produced in activate astrocytes of the spinal cord in the late phase (3 weeks) of nerve injury [56].

Intrathecal infusion of bFGF produces persistent activation of spinal astrocytes through the upregulation of P-JNK and GFAP and sustained mechanical allodynia and chronic pain [56]. On the other hand, intrathecal administration of a bFGF-neutralizing antibody reduces established neuropathic pain [93].

After nerve injury, also proteases are upregulated in spinal glia. It is well known that, spinal nerve ligation induces matrix metalloprotease-2 (MMP-2) in spinal cord astrocytes and DRG and satellite glial cells (SGCs) in the late phase of neuropathic pain to maintain neuropathic state, via activation of IL-1β and ERK [94].

Nerve injury additionally stimulates the production of cathepsin S in spinal microglia [95] and tissue-type plasminogen activator (tPA) in spinal astrocytes to enhance neuropathic pain [96]. A recent study indicated that nerve injury also increased the production of thrombospondin-4 (TSP4), an extracellular matrix glycoprotein, in spinal cord astrocytes correlated for the development of neuropathic pain and for synaptogenesis [97, 98].

To increase and to maintain the pain state, astrocytes produce small molecule mediators such as D-serine, ATP, and glutamate [41].

On the other hand, the anti-inflammatory and antinociceptive mediators IL-4, IL-10, and TGF-β were produced by glial cells for the recovery and resolution of pain [20, 99–102]. Improvement of endogenous production of IL-10 via gene therapy has been demonstrated to produce long-term relief in neuropathic pain. Of interest, a possible off-target effect of high doses of siRNAs is to induce IFN-α in spinal astrocytes for eliciting antinociceptive effects [103, 104].

3.5 Targeting Excessive Inflammation as a Therapy for Neuropathic Pain

There is currently strong suggestion from preclinical studies, and more restricted evidence in clinical studies, that damage to the nervous system can lead to a maladaptive inflammatory reaction contributing to the generation of persistent pain.

There remain various obstacles to making an interpretation of this information into patient benefit. For this reason, there are several challenges in the design of appropriate clinical trials.

Using pain animal models are most successful at the time of injury, while delayed treatment is a more likely clinical scenario. On the other hand, only a subset of patients develop neuropathic pain after a lesion and we do not yet have effective predictive models. Increasingly evidences suggest that there are multiple pathophysiological mechanisms leading to persistent pain after nerve injury. It would be of great benefit to use either clinical or molecular biomarkers to individualize treatment, for example, targeting excessive inflammation only in those patients where there is evidence of an ongoing inflammatory response [105]. Some agents that modulate inflammation are already being used in selected groups of patients with neuropathic pain, although there is often a lack of evidence from the trial. It is well known that corticosteroids suppress pro-inflammatory cytokine expression and cell-mediated immunity. They are administered by several routes for the treatment of several neuropathic pain conditions, such as post-herpetic neuralgia or radicular back pain; however, definitive evidence for their efficacy is absent because of the scarcity of placebo-controlled studies and, in some cases, trials have shown side effects [106–109].

Another approach, recently studied, involved the use of select cytokines inhibitors [110, 111]. One probable trouble is the significant redundancy in the action of cytokines. Furthermore, as with corticosteroid suppression of the immune system, if these agents are given systemically they may be associated with an appreciably amplified risk of infection. The use of pro-resolution agents such as resolvins would be one strategy that could use a wide anti-inflammatory intervention [112].

The inhibition of microglial function is another novel option. Minocycline clinical trials for the prevention of postoperative intercostal pain, an optimal situation for testing this agent, are ongoing (NCT0131 4482).

Propentofylline decreases the production of free radicals and microglia activation. A randomized controlled trial of this agent did not find efficacy in the treatment of post-herpetic neuralgia [62]. Further approaches would be to target key ligand-gated ion channels expressed in microglia such as P2X4 and P2X7 or downstream signaling pathways that drive microglia towards an effector state such as p38 MAP kinase.

In a small double-blind crossover trial, the p38 mitogen-activated protein kinase inhibitor SB-681323 significantly decreased the daily pain score in patients with neuropathic pain [8, 113].

3.6 Clinical Significance and Future Perspectives

The delivery of anti-inflammatory drugs to the CNS is critical, given the significant role of key neuroinflammation in keeping chronic pain. Neuroinflammation consequential from neuroglial and neuro-immune interactions not only assists as a driving force for chronic pain but is also involved in other neurological and

psychiatric diseases such as Alzheimer's and Parkinson's disease, multiple sclerosis (SM), autism, and others, as well as in cognitive deficits after major surgeries [114, 115]. Chronic pain is, in fact, commonly linked with depression, anxiety, sleep disorders, and cognitive decline, which are clinical sequelae of particular concern to the growing aging population which has increasingly high prevalence of chronic pain. Neuroinflammation and astrocyte reactivity is also connected with chronic pain in postmortem human spinal cord samples [116]. The development of effective new treatments for the prevention and resolution of neuroinflammation and postoperative pain is mandatory. Actually to counteract neuroinflammatory processes a new therapeutic approach is represented by the use of natural compound. In this chapter we focused our attention on some recent evidences that involved the use of aliamides, alone, or in association with antioxidant molecules.

3.7 PEA

N-Acylethanolamines are classified as naturally occurring lipidic mediator molecules composed of a fatty acid and ethanolamine, collectively namely "fatty acid ethanolamines" (FAEs). They are endogenous molecules involved in endogenous protective mechanisms, activated in the body as a result of different types of tissue damage or stimulation of inflammatory responses and nociceptive fibers. The members of FAE family are the endocannabinoid N-arachidonoylethanolamine (anandamide, or 5Z,8Z,11Z,14Z)-N-(2-hydroxyethyl)icosa-5,8,11,14-tetraenamide) and its congeners N-stearoylethanolamine (N-(2-hydroxyethyl)-stearamide), N-oleoylethanolamine (N-2-hydroxyethyl- 9(Z)-octadecenamide), and N-palmitoylethanolamine (PEA, or palmitoylethanolamide) (N-(2-hydroxyethyl)- hexadecanamide).

PEA and its congeners are formed from N-acylated phosphatidylethanolamine (NAPE) by several enzymatic pathways [117], the principal one involving a membrane-associated NAPE-phospholipase D which generates the respective NAE and phosphatidic acid. This enzyme is able to convert N-palmitoyl-phosphatidyl-ethanolamine into PEA. In the mammalian brain, NAEs are hydrolyzed by: (1) fatty acid amide hydrolase in the endoplasmic reticulum, which breaks down NAEs into the corresponding fatty acid and ethanolamine; (2) lysosomal NAE-hydrolyzing acid amidase (NAAA) [118]. NAAA is found mainly in macrophages, where it hydrolyzes NAEs with less than 18 carbon atoms, i.e., PEA, but not N-oleoylethanolamine and N-stearoylethanolamine. In contrast, fatty acid amide hydrolase hydrolyzes all three NAEs. PEA is abundant in mammals; there are evidences for the presence of PEA as well as other FAEs in marine species and sea urchin ovaries [119]. Biologically, PEA is produced and hydrolyzed by microglia [120], inhibits mast cell activation [121], and increases in glutamate-treated neocortical neurons ex vivo and in cortex after CNS injury, as well as in muscle dialysate from women with chronic neck/shoulder pain [122].

PEA levels are also increased in a mouse model of experimental allergic encephalomyelitis [123].

Mechanistically PEA may be a ligand for peroxisome proliferator activated receptor α (PPARα), one of a group of nuclear receptor proteins that function as transcription factors regulating the expression of genes. In particular, the α- and γ-isoforms of PPAR are associated with pro-inflammatory effects. Moreover, in PPARα null mice or blocked by PPARα antagonists the anti-inflammatory, antinociceptive/anti-neuropathic, and neuroprotective effect of PEA were not detected [124]. PEA is produced through an *"on-demand"* synthesis within the lipid bilayer where N -phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) releases it from its membrane precursor, N-palmitoyl phosphatidylethanolamine.

An *"entourage effect"* has also been hypothesized to clarify the pharmacological actions of PEA, whereby PEA enhances the anti-inflammatory and antinociceptive activity of other endogenous compounds by potentiating their affinity for a receptor or by inhibiting their metabolic degradation.

Anandamide and its congeners like PEA have in common the transient receptor potential vanilloid type 1 (TRPV1) receptor that is activated by noxious heat, low pH, and capsaicin. Anandamide itself is a TRPV1 receptor agonist, and PEA enhances anandamide stimulation of the human TRPV1 receptor in a cannabinoid CB2 receptor antagonist-sensitive fashion—which could be interpreted as PEA acting indirectly by potentiating anandamide actions. Mast cells and microglia reportedly express TRPV1 receptors [125].

3.8 Polydatin

Polydatin (PO), also called piceid, is a traditional Chinese medicine, detected in many daily diets food that has wide-ranging pharmacological activities [126, 127]. There are four main derivatives of PO in nature, including trans-polydatin, trans-resveratrol, cis-polydatin, and cis-resveratrol [128].

PO has a range of biological effects, such as the ability to protect lung, brain, heart, and intestine against ischemia-reperfusion (I/R) injury, anti-platelet aggregation, as well as anti-inflammatory, anti-shock, and anti-oxidation effects [129–135]. Additionally, two studies done in the last year demonstrated that PO protects against acetaminophen-induced hepatotoxicity in mice and suppresses nucleus pulposus cell senescence, promoting matrix homeostasis and attenuating intervertebral disc degeneration in rats [136, 137].

3.9 PEA and Polydatin as Future Treatment of Chronic Pelvic Pain

Preclinical studies about the management of chronic pain with the association of PEA and PO showed a significant reduction in the inflammatory process and pain associated with an experimental rat model of surgically induced endometriosis or carrageenan-induced acute inflammation as well as possess the ability to decrease

prostate weight, DHT production, inflammation and oxidative stress process and apoptosis dysregulation in an experimental model of testosterone induced benign prostatic hyperplasia [138–140].

Clinical trials in which PEA/PO was first used was published in 2010 [141, 142], suggesting that a combination of micronized PEA/PO was efficient in endometriosis-related chronic pelvic pain. Indraccolo et al. [142] reported only 4 cases of endometriosis treatment with oral micronized PEA/PO (400 mg/40 mg) twice a day for 3 months, while Cobellis et al. [143] treated 18 patients in one arm of a randomized trial with micronized PEA/PO (200 mg/20 mg) orally, three times a day for 3 months. Both studies showed an improvement in mean pain visual analog scale (VAS) scores for chronic pelvic pain and other endometriotic pains (with improvement in the micronized PEA/PO arm versus placebo arm in the randomized trial [143]). The above observations were substantiated by results of VAS score improvement in a study on 610 patients [144] treated with micronized PEA (600 mg twice daily) for chronic pain due to several causes, leading us to speculate that micronized PEA is effective also on chronic pelvic pain, even in the presence of endometriosis.

Additionally, another study provides preliminary evidence on the efficacy and safety of um-PEA/PO as an add-on treatment to conventional pharmacological regimens in patients suffering from IC/BPS, showing a significantly decreased pain in 75% of patients [145].

In another set of experiment, Tartaglia and colleagues considered the effectiveness of an oral combination of PEA and trans-polydatin in the treatment of primary dysmenorrhea in healthy adolescents and young women and found a reduction in symptoms, exerting a neuroprotective and antinociceptive effect during primary dysmenorrhea [146].

Interestingly, all mechanistic studies showing a benefit of active treatment in the management of several pathologies failed to exactly clarify the exact mechanism of action of the active compound, confirming the complexity of these type of studies [147–149]. Whether the PEA/PO effect is centrally related, secondary to mast cell stabilization or to modulation of the endocannabinoid system remains to be further investigated [150, 151].

In fact, confirmation of these initial findings will require randomized, double-blind, placebo-controlled clinical trials of sufficient power to assess rates of respondents in subgroups of patients, in order to fully appreciate the efficacy of micronized PEA/PO combination as a therapy for endometriosis, together with cohort studies to assess long-term effects of such therapy [142].

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