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Chronic pelvic pain, Quality of Life and Sexual Health of women treated with Palmitoylethanolamine and α-Lipoic Acid

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***Aim*. The aim of this paper was to evaluate the effects of the association between palmitoylethanolamine (PEA) and α-lipoic acid (LA) on quality of life (QoL) and sexual function in women affected by endometriosis-associated pelvic pain.**

***Methods*. Fifty-six women constituted the study group and were given PEA 300 mg and LA 300mg twice daily To define the endometriosis-associated pelvic pain, the visual analogic scale (VAS) was used. The Short Form-36 (SF-36), the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS) were used to assess the QoL, the sexual function and the sexual distress, respectively. The study included three follow-ups at 3, 6 and 9 months.**

***Results*. No changes were observed in pain, QoL and sexual function at the 3rd months follow-up (P=ns). By the 6th and 9th months, pain symptoms (P<0.001) and all categories of the QoL (P<0.001) improved. The FSFI and the FSDS scores did not change at the 3 months follow-up (P=ns). On the contrary, at the 3rd and 9th months follow-ups they improved with respect to the baseline (P<0.001).**

***Conclusion*. The progressive reduction of the pain syndrome reported by women over the treatment period could contribute to improve the QoL and sexual life of women on PEA and LA.**

KEY WORDS: Endometriosis - Pelvic pain - Quality of life.

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Chronic Pelvic Pain (CPP) is commonly defined as continuous or intermittent pain located in the lower abdomen and in the pelvic area with cyclical or noncyclical emergence, which often causes functional limitations in daily activities and a reduction of quality of life (QoL). The signs and the symptoms of CPP vary from woman to woman in terms of location and intensity, as well as for the presence or not of urinary disorders and sexual dysfunction.[1] CPP can arise from a multitude of causes in various organ systems; in addition to the gynaecology system, it can also affect the gastrointestinal, neurological and musculoskeletal [2, 3] system, so it often happens that it requires a multi-disciplinary [4] approach.

Ten per cent of women of reproductive age, with a peak of incidence between the ages of 25 and 30 years, suffer from CPP,[5, 6] the emergence of which is often due to the chronic inflammatory reaction of endometrial lesions.[7, 8] The signs and symptoms associated with endometriosis are dysmenor-

TABLE I.—*Pain syndrome before and during treatment with Palmitoylethanolamine and α-Lipoic Acid.*

Disorders	Baseline N. 56	3 months N. 51	6 months N. 46	9 months N. 41
CPP	56 (100%)	28 (54.9%)	13 (28.3%)	7 (17.1%)
Dysmenorrhoea	51 (91.1%)	18 (35.3%)	9 (19.6%)	3 (7.3%)
Dyspareunia	32 (57.1%)	21 (41.2%)	9 (19.6%)	5 (12.2%)

rhoea, deep dyspareunia, painful ovulation, premenstrual or cyclical symptoms with or without alterations in the cycle, dysuria, dischezia, and last but not least infertility.[9, 10] In Italy, 70% of women suffer from CPP and more than 60% suffer from dysmenorrhoea. The symptoms of endometriosis impact on many aspects of QoL, such as work, relationships and social functioning.[11, 12] Endometriosis also affects mental health; indeed, the intensity of pain is related to the level of anxiety and depression.[13] Not least, the women report sexual discomfort, principally dyspareunia.[14]

Laparoscopy is considered the gold standard for the diagnosis of endometriosis; nevertheless the presence of specific symptoms, as well as clinical evidence and non-invasive instrumental diagnostics, such as ultrasound, is often sufficient to make the diagnosis.[15]

CPP associated with endometriosis is a diffuse visceral pain. In the pathogenesis of CPP at least three different mechanisms require consideration: a nociceptive substrate, an inflammatory substrate and a neuropathic substrate, which variously contribute to dysmenorrhoea, dyspareunia and to noncyclical pelvic pain. The involvement of mast cells in all three painful mechanisms has been broadly confirmed. Therefore, the possibility to use a specific approach which normalises mast cell activity is used more and more frequently. Palmitoylethanolamine (PEA) is recognized as a substance able to modulate mast cell activation, with a reduction of pelvic pain.[16-18] PEA inhibits mast cell degranulation, with a consequent reduction in products recognized as having a pro-inflammatory activity. Indeed, the substances freed from mast cell degranulation are able to transform inflammatory pain in neuropathic pain.[19, 20] The anti-inflammatory action of PEA finalized at reducing central and peripheral sensitization is mediated by neuronal and non-neuronal cells.[21-23] Therefore, these abilities of PEA explain its ability to treat different pain and inflammatory disorders.[24]

PEA has proven effective in modulating CPP caused by deep endometriosis and dysmenorrhoea from ovarian endometriosis.[17, 25]

Another substance with an anti-inflammatory, antioxidant, analgesic, neuroprotective action is α-Lipoic Acid (LA).[26] It plays a role in cellular energy metabolism and extends an anti-oxidising activity to free radicals, facilitating proinflammatory effects.[27]

In Italy, the association between 300 mg of micronized PEA with 300 mg of LA as a supplement (PEANASE, LJ Pharma, Catania, Italy) is currently in use. The association has the purpose of intervening to control CPP symptoms, also with multi-organ dysfunction syndrome and systems, through the inhibitory modulation of the mast cell, the control of ROS freed from neurogenic inflammation, the inhibition of spinal microglia activated by the nervous lesion and the blockage of the cyclooxygenase activity of the arachidonic acid cascade.

The aim of this study has been to assess the efficacy of administrating PEA 300 mg in association with LA 300 mg (2 tablets / day) on the QoL and on the sexual health of women suffering from CPP.

Materials and methods

The study protocol conforms to the guidelines of the 1975 Declaration of Helsinki. The informed consent was obtained from each woman before entering the study.

The study was conducted between Jan-

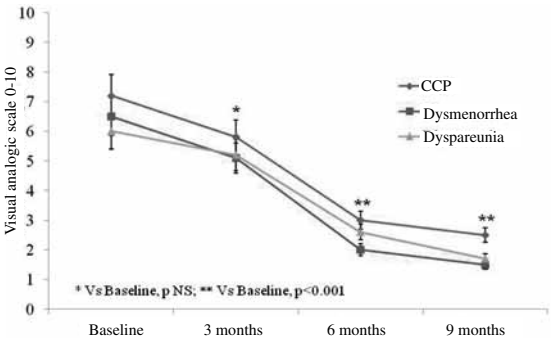


Figure 1.—Visual Analogic Scale (VAS) of women affected by chronic pelvic pain, dysmenorrhoea and dyspareunia before and during treatment with Palmitoylethanolamine and α-Lipoic Acid.

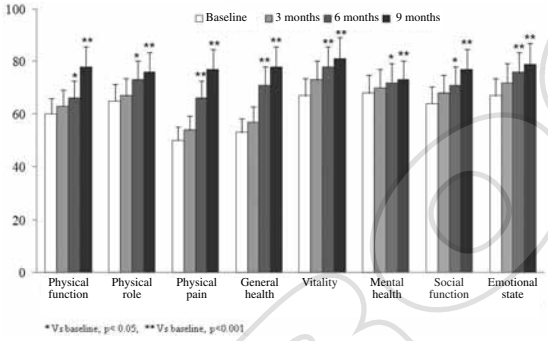
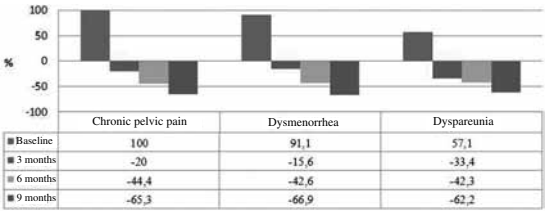


Figure 3.—elvic pain, dysmenorrhea and dyspareunia before and during treatment with Palmitoylethanolamine and α-Lipoic Acid.



	Chronic pelvic pain	Dysmenorrhea	Dyspareunia
Baseline	100	91,1	57,1
3 months	-20	-15,6	-33,4
6 months	-44,4	-42,6	-42,3
9 months	-65,3	-66,9	-62,2

Figure 2.—Variations (%) of the chronic pelvic pain, of dysmenorrhea and of dyspareunia before and during treatment with Palmitoylethanolamide and α-Lipoic Acid.

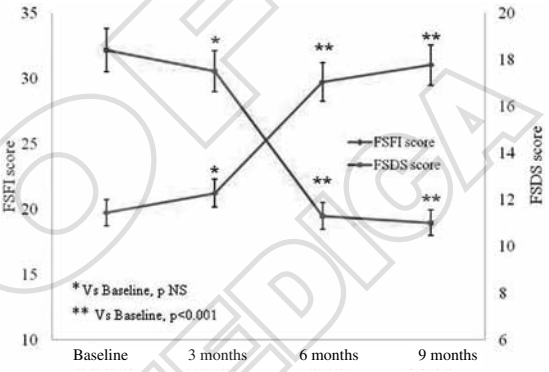


Figure 4.—Female Sexual Function Index (FSFI) and Female Sexual Distress Scale (FSDS) in women with chronic pelvic pain, dysmenorrhea and dyspareunia before and during treatment with Palmitoylethanolamine and α-Lipoic Acid.

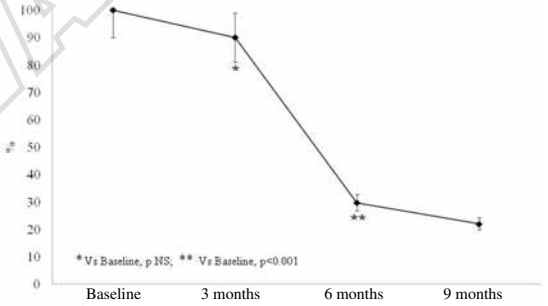


Figure 5.—Frequency of assumption of NSAIDs in women with chronic pelvic pain, dysmenorrhea and dyspareunia before and during treatment with Palmitoylethanolamine and α-Lipoic Acid.

uary 2014 and September 2014. Fifty-six women between the ages of 18 and 31 (average age 26±6) years, affected by CPP, were enrolled in the study after receiving counselling on the benefits of PEA/LA administration. At the enrolment phase the medical and surgical history of each woman was gathered and the women were submitted to clinical gynaecological examination and to trans-vaginal sonography (TVS). Based on the ESHRE [28] guidelines, the women affected by CPP with a clinical diagnosis of endometriosis (dysmenorrhoea, noncyclical chronic pelvic pain, deep dyspareunia, and dyschezia) were submitted to TVS to identify nodes of the recto-vaginal septum, deep endometriosis, ovarian endometrioma or adenomyosis.[29] Furthermore, sexually active women with at least one activity during the month preceding the enrolment were also included. Women with a history of non-organic sexual dysfunction, or with a partner affected by sexual dysfunction, or undergoing treatment with elements similar to GnRH for at least 6 months, or who were users of hormonal or progestin contraceptives for at least three months, were excluded from the study. For ethical reasons and for the treatment proposed, the efficacy of

which is connected to restoring the balance of inflammatory processes, each woman was recommended to continue to use non-steroidal anti-inflammatory drugs (NSAIDs) when necessary.

The visual analogic scale (VAS) [30] was used to define endometriosis-associated pelvic pain. Each woman was taught to mark their subjective perception on the scale with a range from 0 (no pain) to 10 (unbearable pain). The enrolment process envisaged a cut-off >5.

The questionnaire (SF-36) [31] was used to define the QoL. The questionnaire contains 36

questions grouped into 8 categories: physical function (10 items), physical role (4 items), physical pain (2 items), general health (6 items), vitality (4 items), social functioning (2 items), the emotional role (3 items) and mental health (5 items). The women were taught to mark the level of each item which they believed better corresponded to their perception on a scale from 0 to 100. Therefore, the mean value was calculated on the basis of the individual items inside a given category. Consequently 8 scores were obtained, the highest value of which indicates a better function.

The sexual history of each woman was gathered before they began the treatment. To define sexual dysfunction, if present, the classification of the consensus conference on female sexual dysfunction [32] was used. The sexual activity and the behaviour were determined through the Italian validated version [33] of the self-administered questionnaire Female Sexual Function Index (FSFI). The questionnaire comprises six categories: desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items) and dyspareunia (3 items), with a Likert scale based on five variable points of frequency, from 0 (no sexual activity) or 1 (never/very low) to 5 (always/very high).

The score is calculated for each of the six categories and the total score is obtained by summing the single scores. The total score varies from 2 to 36. The cut-off ≤26.55 is usually used to diagnose sexual dysfunction. Furthermore, to diagnose sexual dysfunction, an essential element is that it is associated to the presence of personal distress. Consequently, the Female Sexual Distress Scale (FSDS) [34] was used. The FSDS comprises 12 items. The highest score is 48. One score ≥15 corresponds to one clinical distress. Therefore we considered women with a total FSFI score lower than 26.55 to be suffering from sexual dysfunction if at the same time the FSDS score was higher than 15.

After the pretreatment assessment, each woman included in the study received the prescription of the association of 300 mg PEA and 300 mg LA (1 administration 2 times a day) for 9 months. The study included 3 follow-up sessions, at 3, 6 and 9 months. All the questionnaires were administered, aside from at the pre-treatment phase, at each follow-up session. Finally, each woman was given a diary in which to note, on a daily basis, sexual activity and any adverse events, as well as the assumption of any pain-relieving drug. The Student test was used to compare the pre-treatment values of the VAS and of the SF-36 with those obtained at the follow-up sessions. To compare the FSFI values obtained during the treatment with those of the pretreatment phase the non-parametric Wilcoxon test was used. The values are presented as mean±SD. The results were considered statistically significant when $P<0.05$. The statistical analysis was calculated using the Primer of Biostatics statistical computer Package (Glantz SA, New York, NY, USA: McGraw-Hill, Inc.1997).

Results

Of the 56 women enrolled in the study and to whom the treatment was prescribed, 5 (8.9%), 10 (17.8) and 15 (26.7%) did not present themselves at the follow up of the 3rd, 6th and 9th month. Table I shows the number and percentage of women suffering from CPP and those in which dysmenorrhoea and dyspareunia was associated, at the pretreatment and at the three follow-up sessions. Figure 1 shows how the assump-

tion of PEA/LA had little effect during the first three months of assumption (P=NS); indeed, the VAS score stayed above the cut-off (>5). Conversely, the improvement of the CPP, of the dysmenorrhoea and of the dyspareunia started from the month of assumption (P<0.001). Since the women reported levels of VAS<5 relating to dysuria (3) and dyschezia (1.8) at the enrolment phase the disorders and the values were not reported in the graph.

Figure 2 shows reduction of the pain symptoms in %. Though CPP, dysmenorrhoea and dyspareunia start to diminish from the first three month period (P=NS), the reduction is much more evident at the 6th and 9th month (P<0.001).

Figure 3 shows the changes in QoL during the treatment. At the 3rd month the women showed no improvement (P=NS); conversely at the 6th (P<0.05) and at the 9th month (P<0.001) improvement was reported in all categories.

Figure 4 shows changes observed in sexual health. The total score of the sexual function

(FSFI score) and the distress score (FSDS score) do not change in a statistically significant manner at the 3rd month of assumption (P=NS). At the 6th and 9th month of treatment both scores fall back within the wellness values (P<0.001).

Figure 5 shows the reduction of the use of NSAIDs during the treatment. The percentage of women who give up the use of NSAIDs within the first 3 months (10%) is not statistically significant (P=NS). Conversely, a reduction of 70% at the 6th month and of 78% at the 9th month of treatment (P<0.001) is observed.

Finally, the frequency of sexual activity, highlighted through what was shown on the diary by the women, increased from 2.1 (enrolment) to 4.2 (9th month) (P<0.001).

Discussion

The study is the first to be interested in the efficacy of an association formed by PEA and α-Lipoic Acid to treat CPP associated to endometriosis. The diagnosis of endometriosis was made on the basis of the clinical symptoms and ultrasound diagnostics. For ethical reasons the associated use of NSAIDs to control the pain was maintained. To better define the role of the PEA/LA association, women using hormonal or progestin contraceptives were excluded from the study.

The first interesting data, highlighted by the study, is the latency period required for the PEA/LA association to be effective in controlling pain symptoms. Indeed, during the first three month period of assumption the women drew no benefit, contrary to what was reported by other authors;[17, 25, 35] in these studies the protocol allowed to use hormonal therapy associated with PEA, which contributed to pain control. This evidence focuses the attention on the counselling to adopt during prescription of PEA/LA, the efficacy of which is connected to the time of assumption; indeed, the information on the benefits of the association must be equally finalised at ensuring that the use is continued even if the efficacy tends to delay. Our experience highlights that after the 3rd month it is possible to see the positive effects of the use of PEA/LA, this is probably due to modulation of the mast cell degranulation system and recovery from a painful neuropathic memory.

What we have observed strengthens the recovery times necessary for the woman to experience a better QoL and a pain free sexual life. The improvement of CPP and of the pain symptoms of dysmenorrhoea and dyspareunia triggers positive attitudes on the various aspects of QoL. Sexual function also improves as a consequence of the recovery from the pain symptoms.

Through improvements of sexual function and the synchronous reduction of distress shown by our study, the women resume an improved sexual activity, not just qualitative but also quantitative. Indeed the monthly frequency of sexual activity increases from 2.1 at pretreatment stage to 4.2. in the 9th month. Finally, an important fact is the reduction in the use of NSAIDs of 10%, 70% and 78% respectively at the 3rd, 6th and 9th

month of assumption of PEA/LA. The less frequent use of pain relieving drugs after the first 3 months shows once again the need to wait for the supplement to take effect. Offering information during counselling on the opportunity which the woman will have to reduce or abandon the pain relieving drug can be another reason for them to become attached to the supplement towards which, otherwise, doubt could arise on the efficacy due to the delay in the benefits.

Conclusions

QoL assessment is a crucial parameter to consider before drawing conclusions on the efficacy of a treatment. On the basis of the results obtained, we consider the first three months to be the period during which a series of objective and subjective modifications begins towards a re-conquered balance or balance which is experienced as new.

Today, dienogest is used more and more frequently, by itself or as a contraceptive component,[36-38] to treat CPP related to endometriosis.

Dienogest represents the choice treatment to reduce painful gynaecological symptoms, thanks to its antiproliferative, immunologic and antiangiogenic effects; on the other hand, this is less effective in the case of CPP caused by urologic, gastrointestinal or musculoskeletal disorders, where the PEA/LA is an excellent presidium to recover mast cell activity.[39, 40]

CPP often begins in adolescence, it is neglected, diagnosed late and women frequently

withstand endometriosis through momentaneous wellness obtained by using

pain relieving drugs "when needed".[41, 42] Early diagnosis is essential to affect the progression of the chronification of pain and to preserve future fertility.[43]

It is desirable that the PEA/LA association is started in the adolescent when their gynaecological path appears to be marked by pain symptoms which start to affect their QoL and which envisage the genesis of CPP.

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