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Micronized palmitoylethanolamide/ *trans*-polydatin treatment of endometriosis-related pain: a meta-analysis

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Abstract

Aim. To demonstrate clinical effectiveness of micronized palmitoylethanolamide-trans-polydatin combination in reducing endometriotic chronic pelvic pain. Other endometriotic-pains were also assessed.

Methods. Systematic reviews of PubMed, SCIELO, Scopus, and AJOL. Randomized trials and observational studies reporting a visual analogue scale for pain or similar in endometriotic patients were reviewed. A mean improvement of visual analogue scale (or visual analogue scale-like) scores at enrollment and at a three-month follow-up was assessed and interpreted clinically.

Results. Four studies of poor quality were available. In a heterogeneous sample of endometriotic patients with pain, the administration of micronized palmitoylethanolamide/trans-polydatin (400 mg/40 mg) twice a day for three months provided a clinically relevant improvement of chronic pelvic pain and dysmenorrhea while improving deep dyspareunia to a limited degree. No clinically relevant improvement was found for dyschezia.

Conclusion. More studies are warranted for assessing the drugs-related efficacy.

Key words

- chronic pelvic pain
- dysmenorrhea, dyspareunia
- endometriosis
- palmitoylethanolamide
- polydatin

INTRODUCTION

Endometriosis affects women's health throughout life [1]. With a prevalence of 10% [2], Oppelt *et al.* [3] estimated in-patient treatment costs of endometriosis in Germany for 2006 at € 40 708 716. As endometriosis is a painful syndrome [4, 5] and a common cause of chronic pelvic pain [6-8], considerable therapeutic efforts have been directed to treat endometriosis-associated pain. Chronic pelvic pain in endometriosis is also associated with mood disorders, thereby affecting patient quality of life [9, 10].

Current treatments for endometriotic pain include hormonal therapies (levonorgestrel-releasing intrauterine systems, progestagens, estroprogestinic pills, aromatase inhibitors, gonadotropin-releasing hormone agonists), cyclooxygenase-2 inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDs) [5]. Surgical intervention represents another option for treating pain in endometriosis [5]. However, potential side effects linked to the chronic use of pharmacological therapies and risks of surgical approaches hamper the effectiveness of such interventions, especially in terms of achieving long-lasting pain relief. Clearly, today's therapies for managing endometriosis leave much space for improvement [11, 12] and for the development of more effective drugs for treating endometriotic pain [12, 13].

Endometriosis and inflammation are intricately linked to one another [14]. Inflammatory processes are regulated by mast cells [15-17] which are found close to nerve fibers in endometriotic lesions [18, 19]. Conceivably, mast cell activation may contribute to pain development and hyperalgesia in endometriotic lesions during inflammation [18-21]. Targeting mast cells could thus prove useful for controlling inflammation while providing pain relief in endometriosis [22].

Palmitoylethanolamide (PEA) is a member of the N-acylethanolamine family of fatty acid amides. It is a signaling molecule which is able to down modulate mast

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cell activation and microglial cell behaviors [23-25]. It acts peripherally on the crosstalk between mast cells and nociceptive nerve fibers, and in the central nervous system by reducing central pain hypersensitization associated with the activation of microglia [26, 27]. Transpolydatin (PO) is a precursor of resveratrol. Resveratrol has been shown to bring about regression of endometriotic lesions in experimental models of endometriosis [28], a likely consequence of its strong anti-angiogenic and anti-inflammatory actions [29].

Clinical studies in which PEA/PO was used to treat endometriosis were first published in 2010 [30, 31] and suggested that a combination of micronized PEA/PO is effective on chronic pelvic pain due to endometriosis. Indraccolo *et al.* [30] reported only 4 cases of endometriosis treatment with oral micronized PEA/PO (400 mg/40 mg) twice a day for three months, while Cobellis *et al.* [31] treated 18 patients in one arm of a randomized trial with micronized PEA/PO (200 mg/20 mg) orally, three times a day for three months. Both studies showed an improvement in mean pain visual analogue 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 [31]). The above observations were substantiated by results of VAS score improvement in a study on 610 patients [32] treated with micronized PEA (600 mg twice a day) 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.

Although pre-clinical studies and the few clinical observations have suggested that the micronized PEA/PO combination is effective on pain in endometriosis, some questions come to mind regarding this new pharmacological treatment:

How effective is the combination of micronized PEA/PO on endometriotic chronic pelvic pain? To answer the question, one should assess improvements in VAS (or VAS-like) scores. This matter was evaluated by Jensen *et al.* [33], who demonstrated that a reduction in VAS scores between 35% and 40% (20-30 mm) would be considered of clinical relevance;

To what extent is the micronized PEA/PO combination clinically effective on other acute pains of endometriosis? While there is a reasonable expectation for the miconized PEA/PO combination to be effective on chronic pelvic pain, the effectiveness of the micronized PEA/PO on other acute pains in patients with endometriosis remains unclear;

Does the combination of micronized PEA/PO have a different behavior in sub-groups of patients (age, disease stage, previous surgery, other therapies, other comorbidities, etc.)?

Finally, can the micronized PEA/PO combination modify the natural history of endometriosis? By blocking both inflammation and pain, treatment could modify evolution of the disease.

The current meta-analysis was carried out principally to address the question as to whether or not micronized PEA/PO combination is therapeutically effective on endometriosis-related chronic pelvic pain. The secondary aims will be covered as the data permit.

METHODS

The meta-analysis has been registered on the International Prospective Register of Systematic Reviews (PROSPERO), CRD 42015024671. Electronic resources and library availability were provided by the Sapienza University of Rome, if not freely available online. The present systematic review was prepared by searching (up to 19 July 2015) PubMed, Scopus, AJOL (African Journal online), and SCIELO, using the following key-words: "palmitoylethanolamide" AND "endometriosis", "palmitoylethanolamine" AND "endometriosis", "PEA" AND "endometriosis", "polydatin"AND "endometriosis", "impulsin" AND "endometriosis", "impulsine" AND "endometriosis". Impulsin is the older name of PEA [34]. No language limit or time frame limit was set.

The bibliographic search yielded 46 references from only Scopus and PubMed. After removing duplicates, the references list was reduced to 13. Observational studies and randomized trials enrolling patients with endometriosis and endometriosis-related pain who were treated with a combination of micronized PEA/PO were considered eligible for meta-analysis. The patients must have had a pain assessment (VAS or VAS-like) before starting treatment and at least the same pain assessment during follow-up. No limits were placed on VAS assessment (in particular, no differences between the millimetric or centimetric assessment of VAS). Studies with VAS-like assessments were also considered for inclusion. Based on such criteria, seven studies were eliminated. The remaining six studies [30, 31, 35-38] were also examined for other relevant citations, but none were found. The study of Lo Monte' *et al.* [36] was not considered because of possible case duplication. Further, the report from Cobellis *et al.* [31] was excluded, as it was the only study with micronized PEA/PO (200 mg/20 mg) administered three times a day for three months. Assuming that pain relief is dose-dependent, the latter results cannot be incorporated in the current meta-analysis. We were thus able to consider for meta-analysis four studies [30, 35, 37, 38] with five effect sizes.

A stringent (albeit subjective) quality score was applied to the cited studies, and ranged from + to 4+. The score considered four key items: sample homogeneity, sample number, availability of data, and clarity in presentation. The perfect study should be scored 16+, with a minimum limit for quality of 8+. Even poor quality studies were included in meta-analysis, provided that they were able to satisfy at least one of the questions listed at the end of the introduction section.

Figure 1 schematically summarizes the bibliographic search and study selection. The outcome variable was the mean VAS (or numeric rating scale, NRS) reduction after a three months treatment (delta). For the sake of stringency, VAS (or NRS) score improvements were expressed in centimeters. It is possible to express a pain value of 10 (like 10 cm or 100 mm) for NRS or VAS, because the two have been reported to be about equivalent [39-41], even if NRS produces more variability [41].

Missing data were requested of corresponding authors. If corresponding authors were unable to provide missing data, they were recalculated or estimated. To

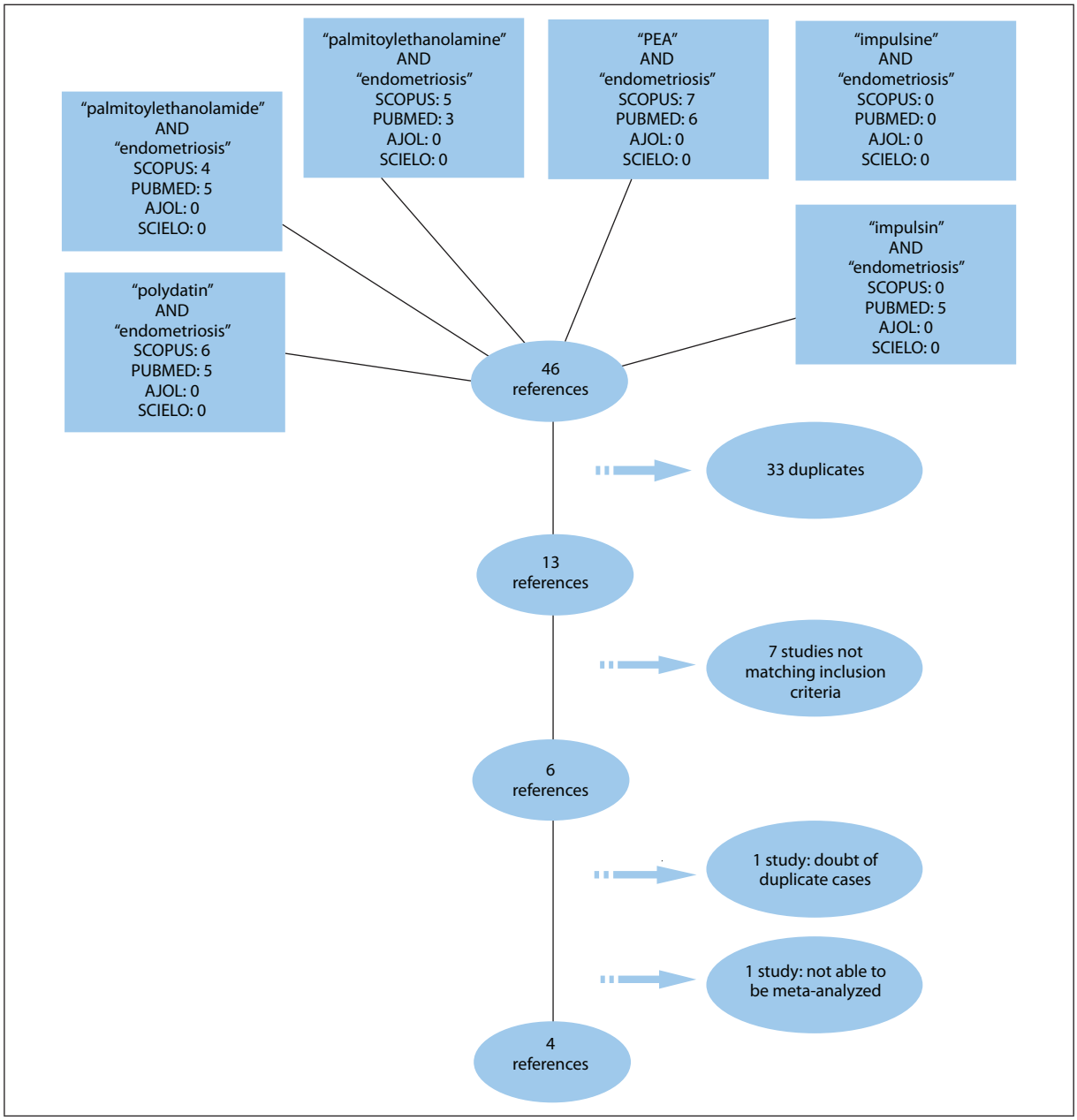

Figure 1
Flow-chart of the phases of study selection.

estimate the delta, we referred to the Lipsey *et al.* rules [42] which imply that standard errors of each delta should be estimated by using already known coefficients of correlation. The latter are calculated from VAS values at enrollment and at the three-month follow-up. Therefore, at least one pool of raw data is needed to calculate coefficients of correlation. As such, only raw data from Indraccolo *et al.* [30] are available for meta-analysis, although they are too few to estimate reliable coefficients of correlation. In order to obtain a more reliable picture of the mean VAS reductions, authors of the cited studies [35, 37, 38] were asked to provide means and standard deviations (or variances or standard errors), calculated on the distribution of delta values. Cobellis *et al.* [35] were unable to provide these data, while Di Francesco *et al.* [38] provided mean and standard deviation of the delta distribution on 9 patients (excluding a patient who had become pregnant before the three-month follow-up), together with missing data on dyschezia. Additionally, Giugliano *et al.* [37] provided means and standard deviations for the VAS reduction distributions (deltas) of their two groups. For the Cobellis *et al.* [35] study, mean effect sizes were estimated from medians according to Hozo *et al.* [43], while variances were estimated from ranges according to Boyles [44] (Median Moving Range Estimator). Ranges and medians were extracted from histograms.

Standard errors were obtained by estimating the coefficients of correlation already cited. Coefficients of correlation were re-calculated from standard deviations

in Di Francesco *et al.* [38] and Giugliano *et al.* (two samples) [37] following Lipsey rules [42]. Mean coefficients of correlation (weighted for the numerosity of the three samples) were used to estimate missing standard errors in Cobellis *et al.* [35] for chronic pelvic pain, dysmenorrhea and deep dyspareunia.

Positive, negative and equivocal findings for endometriotic pain in each study were assessed according to Jensen *et al.* [33]. To be more stringent, a 95% lower confidence interval of more than 3 cm of VAS (or NRS) improvement was considered clinically relevant (positive finding), while a 95% higher confidence interval of VAS (or NRS) improvement of less than 2 cm was taken as no clinical improvement (negative finding). Any mean improvement with a lower or higher 95% confidence interval encompassing or crossing the 2-3 cm range was considered equivocal because of some degree in clinical improvement (equivocal finding).

Fixed models were used for calculating mean effects sizes. Heterogeneity among studies was checked by using Q-statistic. Heterogeneity, when found, was tested by examining if studies with higher VAS (or NRS) values at enrollment had higher VAS reductions (partitioning the effect size variance) [42]. Statistical significance was set at $p < 0.05$.

RESULTS

Table 1 summarizes the characteristics of the four studies included in the meta-analysis and reports results of quality assessment. Only the studies of Cobellis *et al.* [35] and Indraccolo *et al.* [30] reached the minimal limit for quality. The ability of each study to answer the four questions specified in the introduction is also reported in *Table 1*. All studies answered the first question (improvement in chronic pelvic pain) while the meta-analysis was able to partially assess the effect of micronized PEA/PO treatment on the other acute pains of endometriosis (deep dyspareunia, dysmenorrhea, dyschezia). Sub-group analysis was not possible (reply to third question), nor is the meta-analysis able to assess the capability of micronized PEA/PO to modify the evolution of endometriosis (reply to fourth question).

The study by Indraccolo *et al.* [30] is the only one for which raw data are fully available, thereby no missing values must be estimated. While full data availability resulted in data reliability and adequacy for meta-analysis, it is necessary to note that data have been collected on a very limited number of patients (n = 4). VAS improvements are reported as graphical trends and, for chronic pelvic pain, also as mean and standard deviation. However, there is a mistake in the authors' reporting, as the graphical trend and text report for chronic pelvic pain are not congruent. Additionally, results exposition is poor and inaccurate. Further, Indraccolo *et al.* [30] does not provide follow-up data after three months twice daily oral treatment with micronized PEA/PO (400 mg/40 mg). Reduction in analgesic consumption and changes in sonographic patterns of endometriosis were also reported.

Cobellis *et al.* [35] is a randomized, double-blind, three-arm study, designed to prove the superiority of 400 mg/40 mg of micronized PEA/PO orally, twice a day for three months versus celecoxib and placebo. The micronized PEA/PO arm (21 patients) was able to be meta-analyzed after wide estimation of missing values. Diagnosis of endometriosis was made by laparoscopy according to 2005 ESHRE guidelines [4]. Patients had stage I and II endometriosis. The authors reported results at enrollment and after three months follow-up as medians and ranges as histograms for chronic pelvic pain, deep dyspareunia, dysmenorrhea. Self-assessed satisfaction for therapy was reported, but information about long-term follow-up and improvement in instrumental patterns of endometriosis was lacking.

Giugliano *et al.* [37] present an observational, non-randomized, two-arm study, designed to demonstrate that orally administered 400 mg/40 mg micronized PEA/PO twice a day for three months is differentially effective in reducing VAS scores in patients with recto-vaginal endometriosis (group A, 19 cases) versus those with ovarian endometriosis (group B, 28 cases). There were no differences between the two groups. Diagnosis of endometriosis was made by laparoscopic examination, according to 2005 ESHRE guidelines [4]. We cannot exclude that some patients who underwent laparoscopy then received surgical therapy. Data are reported in tabular form as means and standard deviations at enrollment and at each month of follow-up. Long-term follow-up and instrumental improvements of endometriosis were not reported. Both groups A and B were meta-analyzed, and each group was considered as a single effect size.

Di Francesco *et al.* [38] is a randomized, open-label, three-arm study intended to show the effectiveness of 400 mg/40 mg micronized PEA/PO (orally, twice a day for six months, given to 10 patients at enrollment) in controlling the painful symptoms associated with endometriosis in comparison to gonadotropin releasing hormone agonist (GnRh) and estroprogestinic pill. An 11-point NRS (0-10) was used for pain assessment. Endometriosis (stage II and III) was diagnosed laparoscopically with patients required to have at least a pain value ≥ 5 (deep dyspareunia, dysmenorrhea, dysuria, chronic pelvic pain and, perhaps, other kinds of pain related with endometriosis). Results were reported in tabular form at enrollment and graphically as trends in means and standard errors for six-month follow-up. During the study period one patient in the micronized PEA/PO group dropped out because of pregnancy. This study reported on quality of life (SF12 inventory) but lacked information on long-term follow-up and instrumental improvements of the disease. The protocol description and results in Di Francesco *et al.* [38] are confusing. The micronized PEA/PO arm of the Di Francesco *et al.* [38] study was incorporated in the meta-analysis without the pregnant patient (9 cases).

The meta-analysis encompassed 81 patients. For deep dyspareunia and for dysmenorrhea, 80 cases were assessed. For dyschezia, 60 cases were assessed. The mean effect sizes fall into one of three categories: positive, equivocal and negative, in accord with clinical significance assigned to VAS reduction *(Table 2)* [33].

Figure 2 depicts a Forest plot for chronic pelvic pain, with data reported as mean reductions in VAS (or

Table 1
Study characteristics

Study characteristics	Indraccolo *et al.* [30]	Giugliano *et al.* [37]	Cobellis *et al.* [35]	Di Francesco *et al.* [38]
Study type	Small series	Two- arm, prospective, observational study	Three- arm, randomized, double-blind, clinical trial	Three-arm, randomized, open-label, clinical trial
Number of patients	4 patients (mean age 34.3 ± 9.78) 2 clinical and sonographic diagnoses, 2 post-surgery diagnoses	47 patients Post-surgery diagnoses. Group A: 19 patients with recto-vaginal endometriosis (mean age 36.7 ± 5.2). Group B: 28 patients with ovarian endometriosis (mean age 34.6 ± 6.5)	21 patients in the PEA/PO arm, aged between 26 and 37. Post-surgery diagnoses. Stages I and II endometriosis	10 patients in the PEA/PO arm (mean age 33.9 ± 1.61) Post-surgery diagnoses Stages II and III endometriosis. 1 drop-out for pregnancy during therapy
Main objective	Chronic pelvic pain reduction from enrollment to three months follow-up. Patients observed monthly	Check differences in pain reduction between two arms from enrollment to three months Patients observed monthly	Superiority of PEA/PO versus placebo and celecoxib (200 mg twice a day for 7 days for three months) Patients observed at three months follow-up	Non-superiority of PEA/PO *versus* leuprorelin 11.25µg (single administration) and ethinyl-estradiol-drospirenone pill 0.03 mg/3 mg for six months Patients observed monthly
Pain assessment	100 mm VAS	10 cm VAS	10 cm VAS	11 points NRS
Other therapies	1 patient: pill and NSAIDs 3 patients: NSAIDs	Group A 13 patients: pill 6 patients: NSAIDs Group B 18 patients: pill 10 patients: NSAIDs	Not reported	Not reported
Side effects	Nausea	Not reported	Not found	Not found
Pain assessed	Means (± st deviations) VAS at enrollment	Means (± st deviations) VAS at enrollment A B	Medians (and ranges) VAS at enrollment	Means (± st errors) NRS at enrollment*
Chronic pelvic pain	78 (± 13) mm	5.8 (± 2.8) cm 4.6 (± 2.4) cm	7.6 (8.2-6.5) cm	5.3 (± 1.12)
Dysmenorrhea	38 (± 19) mm§	6.5 (± 2.1) cm 6.9 (± 1.6) cm	7.8 (8.8 -6.6) cm	7.5 (± 0.7)
Deep dyspareunia	81 (± 31) mm§	4.1 (± 3.3) cm 3.7 (± 2.9) cm	7.4 (8.4-6.1) cm	5 (± 1.07)
Dyschezia	42 (± 34) mm	4.1 (± 3.4) cm 1.6 (± 2.1) cm	/	0.8 (± 0.80)
Dysuria	42 (± 40) mm§	/ /	/	1.2 (± 0.63)
Secondary findings	Reduction of analgesic consumption Improvement in sonographic patterns of endometriosis	Improvement of pain scores in both arms through months (no differences between two-arm pain improvement)	Improvement of self-reported satisfaction for therapy	Improvement in quality of life (SF-12 inventory)
Quality assessments				
-Homogeneity of sample	+	+	++	+
-Numerosity of sample	+	++	++	+
-Availability of data	++++#	+++	+	++
-Clarity in the exposure of the study (objectives, experimental design, results)	++	+	+++	+
Data availability to meet objectives of meta-analysis				
1) Clinically relevant reduction of chronic pelvic pain	++++	++++	++++	++++
2) Clinically relevant reduction of other endometriosis pain	++++	+++	+++	+++
3) Sub-group analyses	+	+++	/	/
4) Natural history of the disease	+	/	/	/

#This score was given because all raw data of this study are available to the meta-analysts.
§Data from three patients.
*Values extracted from the Di Francesco *et al.* published article – 10 cases [38].

Table 2
Positive, negative and equivocal findings

Study		Improvement not clinically relevant: (negative finding)	Improvement of some clinical relevance: (equivocal finding)	Improvement clinically relevant (positive finding)
Chronic pelvic pain	Indraccolo *et al.* [30]		X	
	Giugliano *et al.*, A [37]		X	
	Giugliano *et al.*, B [37]		X	
	Cobellis *et al.* [35]			X
	Di Francesco *et al.* [38]		X	
Dysmenorrhea	Indraccolo *et al.* [30]		X	
	Giugliano *et al.*, A [37]		X	
	Giugliano *et al.*, B [37]			X
	Cobellis *et al.* [35]			X
	Di Francesco *et al.* [38]		X	
Deep dyspareunia	Indraccolo *et al.* [30]		X	
	Giugliano, A [37]		X	
	Giugliano, B [37]		X	
	Cobellis *et al.* [35]			X
	Di Francesco *et al.* [38]		X	
Dyschezia	Indraccolo *et al.* [30]		X	
	Giugliano *et al.*, A [37]	X		
	Giugliano *et al.*, B [37]	X		
	Di Francesco *et al.* [38] *	X*		

Results from the Di Francesco *et al.* [38] study are on nine patients.
*This effect size can be added because Di Francesco provided unpublished data on the three-month follow-up for dyschezia.

NRS) scores and 95% confidence intervals. Micronized PEA/PO (400 mg/40 mg), given orally twice a day for three months, reduced VAS score by 4.10 cm at the three-month follow-up. This improvement is clinically relevant (95% CI 3.75-4.45 cm, $p < 0.01$, $Q = 39.16$, $p < 0.01$ for four degrees of freedom, indicating heterogeneity). Heterogeneity was resolved by partitioning the variance between two groups (higher and lower VAS or NRS at enrollment). Greater reductions were found in studies [30, 35] with higher VAS scores at enrollment.

Figure 3 depicts a Forest plot for dysmenorrhea. Data are reported as mean reductions of VAS (or NRS) scores and 95% confidence intervals. Micronized PEA/PO (400 mg/40 mg), given orally twice a day for three months, reduced by 3.68 cm the VAS score at three months follow-up. This reduction is clinically relevant (95% CI 3.33-4.03 cm, $p < 0.01$; $Q = 15.94$, $p < 0.05$ for four degrees of freedom, indicating heterogeneity). Heterogeneity was resolved by partitioning variance between the two groups (higher and lower VAS or NRS at enrollment). Greater reductions were found in studies [35, 38] with higher VAS scores at enrollment.

Data for deep dyspareunia are depicted as a Forest

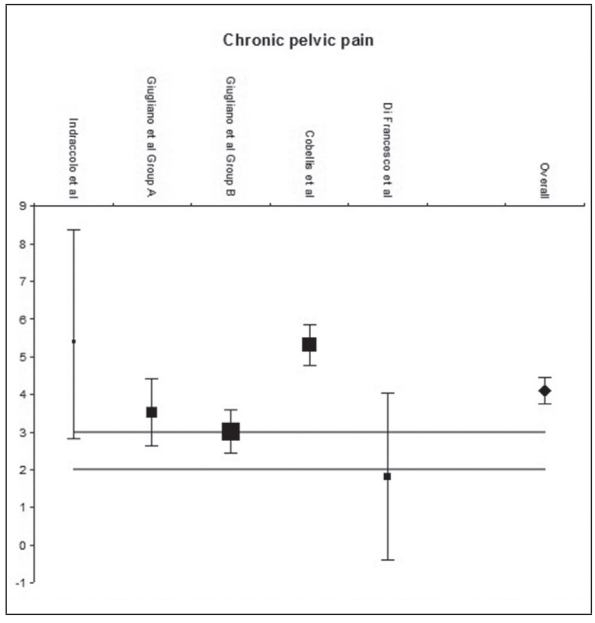

Figure 2
Forest plot for chronic pelvic pain. The horizontal lines define the interval to retain VAS improvements of some clinical relevance.

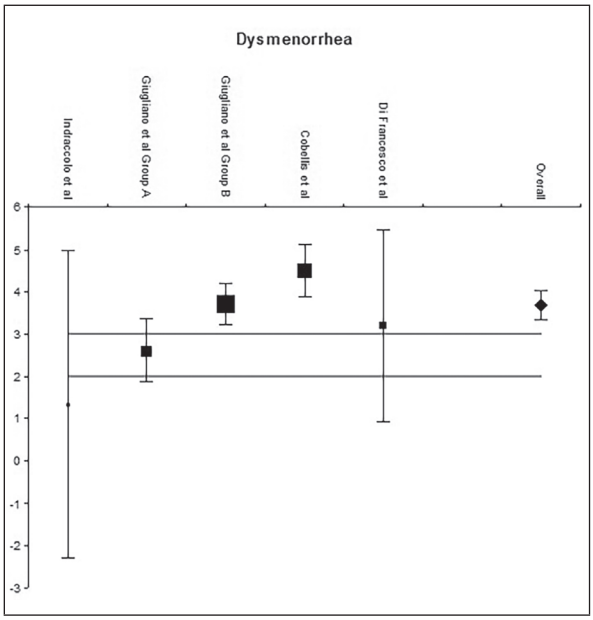

Figure 3
Forest plot for dysmenorrhea. The horizontal lines define the interval to retain VAS improvements of some clinical relevance.

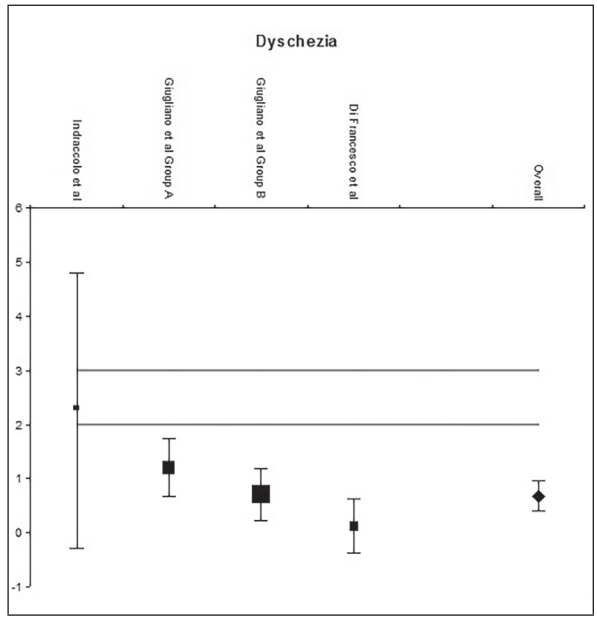

Figure 5
Forest plot for dyschezia. The horizontal lines define the interval to retain VAS improvements of some clinical relevance.

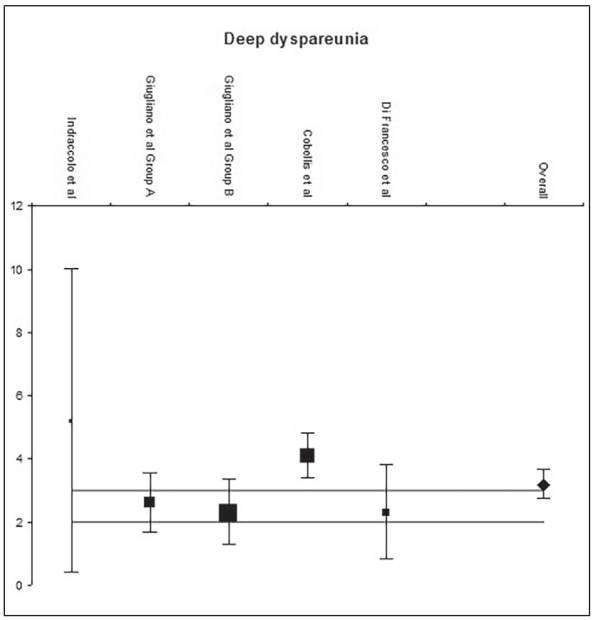

Figure 4
Forest plot for deep dyspareunia. The horizontal lines define the interval to retain VAS improvements of some clinical relevance.

plot in *Figure 4*, and reported as mean reductions of VAS (or NRS) scores and 95% confidence intervals. Micronized PEA/PO (400 mg/40 mg), given orally twice daily for three months reduced by 3.18 cm the VAS score at three-month follow-up. It is unclear if this reduction is always clinically relevant (95% CI 2.71-3.65 cm, $p < 0,01$; $Q = 14.63$; $p < 0.05$ for four degrees of freedom, indicating heterogeneity). Heterogeneity was resolved by partitioning variance between the two groups (higher and lower VAS or NRS at enrollment). Greater reductions were found in studies with higher VAS scores at enrollment [30, 35].

Figure 5 depicts a Forest plot for dyschezia. Data are reported as mean reductions of VAS (or NRS) scores and 95% confidence intervals. Micronized PEA/PO (400 mg/40 mg), administered orally twice a day for three months, reduced by 0.67 cm the VAS score at three-months follow-up. Although this difference was statistically significant, VAS reduction was not clinically relevant (95% CI 0.38-0.96 cm, $p < 0.01$, $Q = 15.25$ $p < 0.05$ for three degrees of freedom, indicating heterogeneity). Heterogeneity was not resolved by partitioning the effect size variance among two groups (higher and lower VAS or NRS at enrollment).

Because results are provided encompassing the estimates from Cobellis *et al.* [35], we also provide results without use of such estimates *(Table 3)*.

DISCUSSION

This meta-analysis demonstrates that, in a heterogeneous sample of endometriotic patients with endometriosis-related pain, the combination of micronized PEA/PO (400 mg/40 mg) administered orally twice a day for three months produces a clinically significant reduction in chronic pelvic pain and dysmenorrhea and a more modest, but significant reduction, in deep dyspareunia. No clinically significant reduction was found for dyschezia.

These results are drawn from poor quality studies, which do not report the rate of respondents. This makes not possible to gather information concerning clinically relevant improvement at patient's level. Therefore, the alleged drugs' efficacy could be only presumed by the mean effect that the micronized PEA/PO had on treated patients. It is conceivable that in a heterogeneous population of endometriotic patients, some could respond to

Table 3
Results without estimates of Cobellis *et al.* [35]

	Chronic pelvic pain	Dysmenorrhea	Deep dyspareunia	Dyschezia
Cases	60	59	59	60
Mean effect size 95% CI	3.14 2.67-3.61	3.32 2.91-3.73	2.48 1.85-3.11	0.67 0.38-0.96
Standard error	0.24	0.21	0.32	0.15
Standard deviation	± 1.89	± 1.64	± 2.46	± 1.15

therapy with robust reductions in VAS scores, while others fail to respond – thus leading to the observed mean VAS improvement. Another possibility is that the majority of endometriotic patients with pain improve their pain perceptions in a clinically significant way, thereby producing the mean VAS reduction. Accordingly, as suggested by sensitive analysis, the best responders should be patients with higher values of VAS (or NRS) scores at enrollment. Such behavior can be expected from any pain-killer drug. Concerning chronic pelvic pain, VAS improvement agreed with reports in other large samples of patients with chronic pain (mostly neuropathic pain) treated with only micronized PEA [32, 45]. Therefore, it is likely that micronized PEA exerts its main effectiveness on chronic pelvic pain, rather than PO. Additionally, it is likely that PEA is more effective than placebo, as suggested by the randomized trials of Cobellis *et al.* [31, 35], which are in agreement with the findings of the large randomized trial of Guida *et al.* [45].

It is unclear if the improvement in VAS for all acute pains of endometriosis can be attributed to the improvement in chronic pelvic pain. It cannot be excluded that PEA, by acting on peripheral and central sensitization mechanisms [46-48] in chronic pain prevents worsening of acute pain over the long-term. However, PO may, in part, also contribute to the observed therapeutic effectiveness. Addressing these issues and quantifying the percentage of respondents (efficacy) will necessitate studies on sub-groups of endometriotic patients with VAS scores at enrollment ≥ 5 cm for acute pains and without clinically significant chronic pelvic pain.

The present meta-analysis fails to investigate changes in the natural course of endometriosis, as a follow-up of more than 6 months was not reported. Improvements in VAS scores have been reported from enrollment to six-month follow-up [38] and evidence for improvement in instrumental patterns of endometriosis is suggested [30]. However, these findings are too limited to permit speculation on changes in the natural history of endometriosis.

Studies on the combination of micronized PEA/PO for treatment of endometriosis reported in databases other than PubMed, AJOL, SCIELO and Scopus were not investigated. This limitation may introduce a degree of bias in our meta-analysis. However, meta-analyzed studies used same kind of 400 mg/40 mg micronized PEA/PO combination. Micronized PEA/PO combination is provided by an Italian manufacturer. It is currently unlikely that the same micronized 400 mg/40 mg PEA/PO was used in studies eventually published in other countries than Italy.

CONCLUSION

In conclusion, in a heterogeneous sample of patients with endometriotic pains, the 400 mg/40 mg combination of micronized PEA/PO, given orally twice a day for three months should be considered a promising treatment for the relief of endometriosis-associated pain. Confirmation of these initial findings will require randomized, double-blind, placebo-controlled clinical trials of sufficient power to assess rates of respondents in sub-groups 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.

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Conflict of interest statement

The authors have no conflict of interest to disclose.

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