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Systematic Review and Meta-Analysis

Antioxidant Agent to Improve Endometriosis Related Pain (Dysmenorrhea, Dyspareunia, Pelvic Pain): A Systematic Review and Meta-Analysis

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KEYWORDS
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ABSTRACT

Introduction: Endometriosis is a chronic condition characterized by the presence of endometrial-like tissue outside the uterus, which causes estrogen-induced inflammation. Pelvic severe pain, dysmenorrhea, and dyspareunia are known as the most common symptoms in endometriosis patients. Antioxidants can help alleviate endometriosis-related pain. However, the mechanism is not fully understood. A study is needed to elucidate the inherent potential of an antioxidant in women with endometriosis.

Material and Methods: The literature search was conducted in two databases. The outcome of interest is to measure mean changes based on pain severity using the VAS score in endometriosis-related pain, including dysmenorrhea, pelvic pain, and dyspareunia. Some of the antioxidant agents formed in this study are vitamin D, vitamin C, vitamin E, livergol (silymarin), garlic tablets, resveratrol, and melatonin compared to placebo. Meta-analysis was done using RevMan 5.4 using mean change from baseline data with their 95% confidence intervals (CI) provided.

Results: Twelve studies meeting the inclusion criteria were considered relevant for assessing the potencies of antioxidants in endometriosis patients (n=695). The antioxidant group had significantly better pelvic pain improvement (MD: -2.21, 95%CI: -3.40 to -1.03, p=0.0003), reduction in dyspareunia symptoms (MD: -1.47, 95% CI: -2.68 to -0.27, p=0.02) as well as improvement in dysmenorrhea with a mean difference -1.92 (95% CI: -3.41 to -0.43, p=0.01) than the placebo group. Antioxidants showed excellent potential to be an alternative treatment in managing endometriosis-related pain, particularly pelvic pain, dyspareunia, and dysmenorrhea.

Conclusion: The efficacy of antioxidant agents can be a potential treatment to alleviate pain associated with endometriosis, such as pelvic pain, dysmenorrhea, and dyspareunia.

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INTRODUCTION

Endometriosis is a chronic condition characterized by the presence of endometrial tissue outside the uterus [1]. It is considered an estrogen-dependent disorder that affects women during their reproductive years. Endometriosis is linked to infertility [2], although typically manifesting as discomfort in the form of dysmenorrhea, dyspareunia, and pelvic pain. Other symptoms include dyschezia and dysuria in people with bowel or bladder involvement. Despite the great variety in the recommendations and methodological quality of the guidelines for endometriosis, several guidelines concur that despite the availability of surgical management options, this chronic illness requires long-term medical care. The control of symptoms is the major objective of endometriosis treatment [3].

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and biological antioxidants, is believed to be a key factor in

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endometriosis pathophysiology. By nature, endometriotic cysts produce a hazardous environment that exposes ovarian tissue to high concentrations of reactive oxygen species, inflammatory cytokines, and proteolytic enzymes [4]. As a result, elevated levels of oxidative stress led to oocyte apoptosis and decreased fertility [5]. On the other hand, when neutrophils and macrophages are active in response to ectopic endometrial tissue, reactive oxygen species are produced by immune cells, and oxidative stress levels rise [6]. Thus, in oxidative stress conditions, a sufficient supply of neutralizing antioxidants is crucial to prevent damage to the immune cells.

Recently, there has been increased interest in the efficacy of antioxidant therapy in treating severe pain symptoms in endometriosis patients, such as persistent pelvic pain, dysmenorrhea, and dyspareunia. It has been shown that using antioxidants can help patients with endometriosis. Cerum oxide nanoparticles, resveratrol, vitamin E, vitamin C, and epigallocatechin-3-gallate (EGCG) were among the antioxidant agents that were frequently used. Research conducted by Amini et al. and Mirzaei et al. demonstrated that a combination of 1000 mg/day of vitamin C and 800 IU/day of vitamin E, or 140 mg of livergol, for a period of 12 weeks significantly alleviated pelvic pain, dysmenorrhea, and dyspareunia ($p<0.05$) [7,8]. Nodler et al study, on the other hand, discovered no significant impact on it [9]. Therefore, a study is needed to elucidate the inherent potential of an antioxidant in women with endometriosis.

Zheng et al.'s recent systematic reviews and meta-analyses highlight antioxidants' potential in reducing endometriosis pain. However, the number of studies included was limited, still relying on older literature, and only included vitamins as an antioxidant agent [10]. Thus, utilizing the most recent literature with various types of antioxidant agents, this study is to provide a systematic review and meta-analysis to determine the potencies of antioxidant supplementation on endometriosis related pain including pelvic pain, dysmenorrhea, and dyspareunia.

MATERIAL AND METHODS

Literature Searching

The following databases were searched using ScienceDirect and PubMed. The following Medical Subject Heading (MeSH) terms were entered individually or in combination in the search: “Antioxidant” AND (“Endometriosis” OR “Endometrioma”) AND “Pain” for this evaluation, all publications articles were published in the last ten years. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria

Before the literature search was conducted, inclusion and exclusion criteria were determined to increase the specificity of the review.

The inclusion criteria were :

1. Randomized controlled trial or clinical trial studies
2. Published in the last ten years
3. The sample population includes patients with endometriosis that use antioxidant agents as the intervention and patients with endometriosis that use a placebo as the control group
4. Having the same unit of measurement (VAS Score)

Exclusion criteria were adopted:

1. Review articles/case series, letter in response, and conference abstract
2. Patients with comorbidities
3. Non-human trials and studies
4. Non-English studies

Data Extraction and Analysis

The selected studies were extracted independently by two authors into a Google Sheet, after which all authors assessed their eligibility and accuracy. Disagreements that occurred during the writing process were resolved through discussions.

Statistical Analysis

We compile the relevant research for each trace element in Microsoft Excel. The potencies of antioxidant supplements in improving endometriosis related pains (chronic pelvic pain, dyspareunia, dysmenorrhea) were evaluated statistically using Review Manager (RevMan) v.5.4 and standardized mean difference (SMD) with a 95% confidence interval (CI). To measure heterogeneity, I2 was utilized. Low heterogeneity was defined as an I2 of less than 25%, moderate heterogeneity as an I2 of between 25% and 75%, and high heterogeneity as an I2 more significant than 75%. A random-effects model was used in the research population was highly diverse. Significant P values are those with a value less than 0.05. Additionally, a subgroup analysis was conducted to examine potential variables that may significantly affect between-study heterogeneity if sufficient studies were available.

RESULTS

Overview of Literature Searching

After the literature search, 161 articles studies identified through database searching from Pubmed and Science Direct. Several articles were excluded due to duplication of studies (n = 30). There are 117 articles

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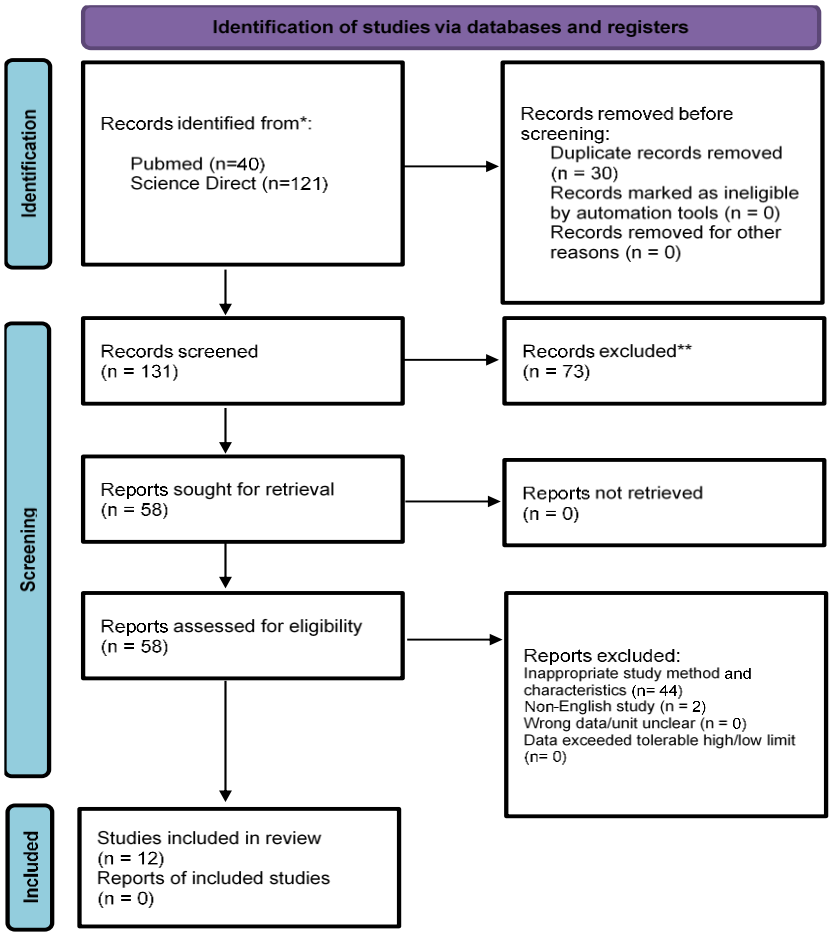


Fig. 1. PRISMA Flowchart of the Literature Selection

excluded due to ineligible data, such as review articles and books, and inaccessible articles due to subscriptions. Fig. 1 shows the PRISMA flowchart. Thus, twelve articles were included in the systematic review and were analyzed in meta-analysis quantitatively and the rest of the studies were analyzed qualitatively.

Study Characteristics

This review included twelve randomized controlled trial (RCT) studies. 695 individuals participated in the research, receiving either antioxidants or a placebo to assess their potencies for improving endometriosis-related pain. The included study used various types of supplements with high antioxidant properties, such as vitamin D, vitamin C, vitamin E, livergol (silymarin), garlic tablets, resveratrol, and melatonin capsules and tablets. Antioxidant interventions and placebos were administered for an average of 6-8 weeks, and the primary observed outcome was a reduction in pain represented by mean changes. Mean changes refer to the alterations in pain sensation from pre- to post-intervention. Studies are summarized in Table 1.

Meta-analysis of Antioxidant Potential vs Control in Endometriosis-Related Pelvic Pain

In this subgroup analysis, nine studies compared the pelvic pain improvement in endometriosis between the antioxidant group and placebo. Antioxidants significantly reduced pelvic pain two times better than the placebo group (MD: -2.21, 95% CI: -3.40 to -1.03, p=0.0003), respectively. Based on the analysis, antioxidant was proven to be superior and could improve pelvic pain better compared to placebo, as illustrated in Fig. 2.

Meta-analysis of Antioxidant Potential vs Control in Endometriosis-Related Dyspareunia

In this subgroup analysis, eight studies examined the improvement of dyspareunia in endometriosis patients with antioxidants compared to a placebo. The application of antioxidants resulted in a statistically significant reduction in dyspareunia symptoms, proving to be 1.5 times more effective than the placebo group (MD: -1.47, 95% CI: -2.68 to -0.27, p=0.02). The analysis suggests that antioxidants offer a more

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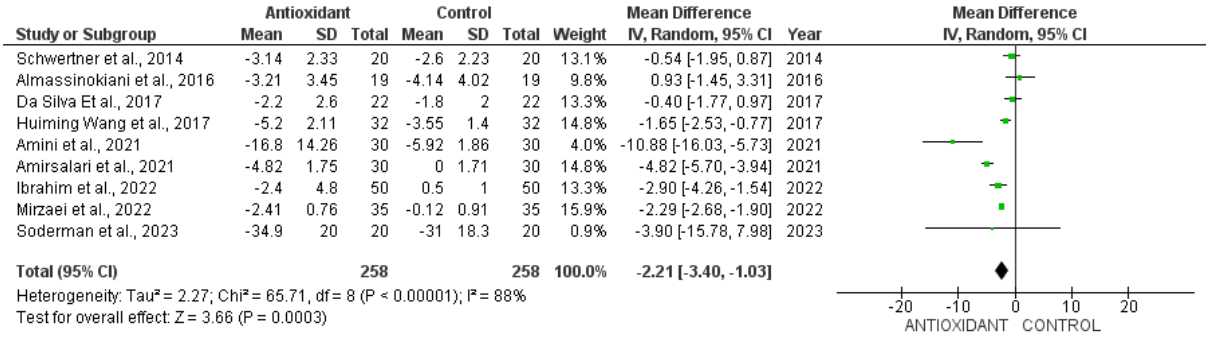


Fig. 2. Mean Differences of Antioxidant vs Control Group for Pelvic Pain Improvement in Endometriosis

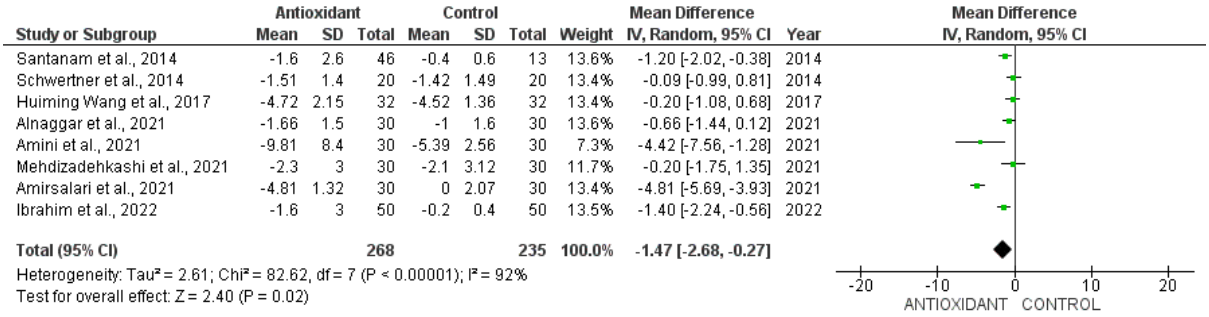


Fig. 3. Mean Differences of Antioxidant vs Control Group for Dyspareunia Improvement in Endometriosis

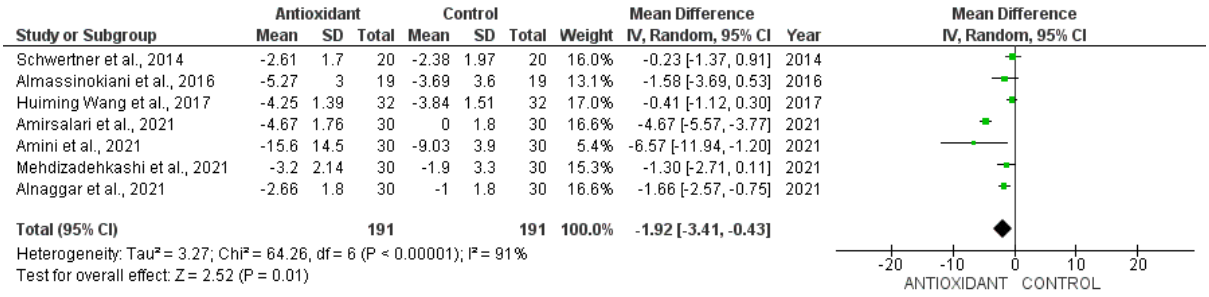


Fig. 4. Mean Difference of Antioxidant vs Control Group for Dysmenorrhea Improvement in Endometriosis

substantial improvement in alleviating dyspareunia symptoms than the placebo, as illustrated in Fig. 3.

Meta-analysis of Antioxidant Potential vs Control in Endometriosis-Related Dysmenorrhea

In this subgroup analysis involving seven studies on endometriosis, the use of antioxidants demonstrated a significant reduction in dysmenorrhea symptoms. The effectiveness of antioxidants was found to be twice as high as that observed in the placebo group (MD: -1.92, 95% CI: -3.41 to -0.43, p=0.01). The analysis supports the conclusion that antioxidants offer a more substantial improvement in alleviating endometriosis related pain symptoms compared to the placebo (Fig. 4). Therefore, these findings highlight the effectivity of antioxidants as an alternative in endometriosis patients.

DISCUSSION

About 75–80% of individuals with endometriosis experience clinically significant symptoms [11]. A prior study revealed a connection between endometriosis and elevated levels of oxidative stress, along with an abnormal increase in reactive oxidative species (ROS) [12]. ROS, which are unstable molecules, engage with

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biological molecules, triggering apoptotic mechanisms and cell death [13]. Antioxidants have been employed to alleviate pain in various conditions, demonstrating their ability to reduce nociception mediated by free radicals [14]. Existing literature on antioxidant therapy indicates that the positive attributes of antioxidants may alleviate symptoms of endometriosis-related pain and mitigate oxidative damage [15].

Ongoing research examines the antioxidant properties of vitamin E, C, epigallocatechin-3-gallate (EGCG), resveratrol, melatonin, and cerium oxide nanoparticles. Our study reveals that the use of antioxidant supplements for 6-8 weeks significantly decreases pain associated with endometriosis, including dysmenorrhea, dyspareunia, and pelvic pain, nearly twice as much as observed in the control group. Supported by a previous study, which found that individuals with endometriosis exhibit lower serum levels of vitamins A, C, and E compared to control groups, possibly stemming from antioxidant consumption during oxidation reactions [4,13,16].

Both animal and human studies indicate that consuming fruits, vegetables, or antioxidant supplements can effectively decrease oxidative stress markers [14,17–19]. For example, a study by Mier-Cabrera et al., demonstrated that vitamins C and E supplementation resulted in a decrease in oxidative stress markers (MDA and lipid hydroperoxides) in women with endometriosis [18]. Ciavatini et al. conducted a study examining the serum vitamin D levels in women with isolated unilateral ovarian endometrioma. In cases of vitamin D deficiency, the findings indicated an 85.7% increase in the size of endometriomas, reaching 40.2±22.6 mm. This was in contrast to cases with normal reference values, where the size was 26.7±12.1 mm [20].

Several studies propose that vitamin deficiency correlates to various gynaecological disorders. There is a notable association between vitamin D insufficiency and the severity of endometriosis in patients. A study by Amini et al. noted a significant reduction in levels of malondialdehyde (MDA) and reactive oxygen species (ROS) using a combination of vitamins C and E [7]. However, there was no change in total antioxidant capacity (TAC) levels when compared to the placebo group.

Additional research conducted by Maia et al. demonstrated that the use of resveratrol resulted in decreased pain in response to this compound [4,21]. Resveratrol, identified as an antiproliferative agent and antioxidant in grapes and red wine, exhibited significant benefits [4]. In a study by Ricci et al., 56 mice with endometriosis were treated with resveratrol for four weeks, leading to a notable reduction in the mean number and volume of established lesions ($P<0.01$) [4]. Furthermore, the treatment effectively decreased cell proliferation lowered vascular density, and significantly increased apoptosis ($p<0.01$). Another naturally produced substance, melatonin, is also suggested to have potent effects on endometriotic lesions. Melatonin, known for its various properties, such as free radical scavenging and the stimulation of antioxidants, has been studied by Yilmaz et al. in the context of endometriosis [13,22,23]. Their research involving twenty rats with endometriosis indicated that melatonin treatment significantly reduced lesion volume and weight ($p<0.05$), suggesting a regression of lesions [15]. Similar efficacy was observed with other antioxidants. However, divergent results have been reported in some studies, such as one examining the impact of vitamin D on endometriosis-related pain, which found no significant effects on pain scores compared to a placebo [7]. These discrepancies among studies may be attributed to variations in study design, patient clinical characteristics, supplement dosage, and intervention duration.

This study exhibited notable strengths, including its basis on data from randomized controlled trials (RCT) with a large population sample. Additionally, evaluating specific outcomes through a comprehensive review of numerous articles enhances the study's ability to provide a holistic perspective and minimize selection bias. Furthermore, this review includes updated literature within the last decade adds to the study's relevance. However, certain limitations should be acknowledged. The varied types and doses of antioxidants used in most studies make it challenging to determine the most effective antioxidant agent. Heterogeneity from disparities in types and doses of intervention could also introduce bias, and the lack of analysis on confounding factors such as diets represents a potential limitation. Despite these limitations, the study convincingly demonstrated the potential of antioxidants as an alternative treatment for managing endometriosis-related pain, particularly in addressing pelvic pain, dyspareunia, and dysmenorrhea.

CONCLUSION

In summary, endometriosis is a chronic medical condition that not only has negative impacts on reproductive health but also diminishes the quality of life due to the pain experienced, delays in diagnosis, the need for ongoing treatment, and high rates of recurrence. In this study, the efficacy of antioxidant agents can be considered as a potential treatment to alleviate pain associated with endometriosis, such as pelvic pain, dysmenorrhea, and dyspareunia.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Table 1. Characteristics of the Included Study

No	Study	Study Design	Sample	Type & Duration of Intervention		Primary Outcomes					
						Pelvic Pain		Dyspareunia		Dysmenorrhea	
				Intervention	Placebo	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)
1	Almassinokiani et al., 2016 [17]	RCT	38	Vitamin D 50 000 iu/weekly for 12 weeks	One placebo capsule for 12 weeks	3.21/3.45	4.14/4.02	-	-	5.27/3.03	3.69/3.6
2	Amini et al., 2021 [7]	RCT	60	Vitamin C (1000 mg/day, two tablets of 500 mg + vitamin E (800 IU/day)	One placebo capsule for eight weeks	16.8/14.26	5.92/1.86	9.81/8.4	5.39/2.56	15.61/14.56	9.03/3.93
3	Mehdizadehkashi et al., 2021 [24]	RCT	60	50,000 IU vitamin D for 12 weeks	One placebo capsule for 12 weeks	-	-	2.3/3	2.1/3.12	3.2/2.14	1.9/3.31
4	Mirzaei et al., 2022 [8]	RCT	70	Two tablets of Livergol 140 mg for 12 weeks	One placebo capsule for 12 weeks	2.41/0.76	0.12/0.91	-	-	-	-
5	Alnaggar et al., 2021 [25]	RCT	60	Vitamin E 3x/day 400 mg + Vitamin C (1000 mg) for 8 weeks	One placebo capsule for eight weeks	-	-	1.66/1.5	1.0/1.6	2.66/1.8	1.0/1.8
6	Huiming Wang et al., 2017 [10]	RCT	64	Vitamin E 100mg/day for 6 months	Placebo for six months	5.2/2.11	3.55/1.4	4.72/2.15	4.52/1.36	4.25/1.39	3.84/1.51
7	Amirsalari et al., 2021 [26]	RCT	60	400mg of garlic tablets for eight weeks	One placebo capsule for eight weeks	4.82/1.75	0.0/1.71	4.81/1.32	0.0/2.07	4.67/1.76	0.0/1.80
8	Santanam et al., 2014 [16]	RCT	59	Vitamin E 3x/day 400 mg + vitamin C 1000 mg for 8 weeks	One placebo capsule for eight weeks	-	-	1.6/2.6	0.4/0.6	-	-
9	Ibrahim et al., 2022 [27]	RCT	100	Vitamin E (1200 mg/day) + vitamin C (1000mg/day) for 8 weeks	One placebo capsule for eight weeks	2.4/4.8	0.5/1.0	1.6/3.2	0.2/0.4	-	-
10	Da Silva Et al., 2017 [28]	RCT	44	Resveratrol 40 mg for 21 days	21 placebo capsules 40mg	2.2/2.6	1.8/2.0	-	-	-	-
11	Soderman et al., 2023 [29]	RCT	40	four capsules of 5 mg melatonin for two months	Four placebo capsules for two months	34.9/20	31/18.3	-	-	-	-
12	Schwertner et al., 2014 [30]	RCT	40	10-mg melatonin tablets for eight weeks	One placebo capsule for eight weeks	3.14/2.33	2.60/2.23	1.51/1.40	1.42/1.49	2.61/1.71	2.38/1.97

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