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MANAGEMENT STRATEGIES OF THE SYMPTOMATOLOGY AND PATHOLOGY ASSOCIATED WITH MENOPAUSE – AN OVERVIEW

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Abstract: *Menopause is a physiological period, considered to be installed after at least 12 months without menstruation. The mean age at menopause is 51 years. This condition is the consequence of hormonal imbalance that produces a series of general manifestations, which have become increasingly important and in most of the cases require treatment to improve. This paper aims to analyze all the therapeutical strategies applied for the improvement of the menopausal symptomatology. After a review of the last five years literature, we identified epidemiological studies, clinical cases, guidelines, and meta-analysis regarding the proper management strategies for the symptoms and pathologies associated with menopause. Fifty-three studies have been included in this paper that provides an overview of the impact of various menopause therapies. Vasomotor symptoms (VMS), hormonal replacement therapy (HRT), consisting of the administration of estrogen, alone or combined with progesterone, have been demonstrated to reduce their frequency and severity. Also, systemic estrogen therapy has shown its efficiency in depression, genito-urinary syndrome, cognitive disorders, and postmenopausal migraine syndrome. Non-hormonal treatments, including alimentary supplements, proved their efficacy with low rates of adverse effects. Among nonhormonal therapeutical alternatives, antidepressants such as venlafaxine, paroxetine, or fluoxetine (selective serotonin reuptake inhibitors - SSRI), and the anticonvulsant gabapentin have shown their utility for treating depressive disorders and vasomotor symptoms.*

Keywords: *menopause, vasomotor symptoms, hot flushes, migraine, genito-urinary syndrome.*

1. Introduction

Menopause is a physiologic period, which coincides with the end of the reproductive period, and is marked by high variability of the symptomatology.

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Also, a wide range of specific pathologies is associated with this period. Depending on their severity, these symptoms can adversely affect the personal and sexual life of patients included in this category. Vascular disorders such as hot flush symptoms, nocturn sweats, palpitations or sleep disorders, migraine syndrome, genito-urinary syndrome, osteoporosis, and sexual disorders (mainly due to vulvovaginal atrophy) are the most common. Among these, VMS affect approximately ¼ of peri- and postmenopausal women, lowering the quality of life of these patients. In most cases, these disorders require treatment to improve [24].

The management strategies for these symptoms and pathologies include hormonal (HRT) or non-hormonal treatment, as well as non-medical (surgical) treatment. HRT is the most efficient therapies, especially for the improvement of VMS. However, researchers showed that they are effective in improving vulvovaginal atrophy complaints, sleep disorders, and general life's quality [24].

Although the effectiveness of hormonal treatment is undeniable, there are some patients for whom this treatment is inadequate due to its contraindications and potential adverse effects, such as cardiovascular disorders or breast cancer [32, 45]. In such cases, non-hormonal treatments and non-pharmacological treatments may be instituted. According to some studies, approximately 40-50% of Western countries women choose to use complementary treatments like herbal remedies in order to improve postmenopausal symptoms and the quality of their life (QoL) [19].

Regarding the effectiveness of non-hormonal or complementary treatments, most have a brief time of action. So, if no improvement of the symptomatology is remarked during the first 2 to 4 weeks of administration, a different approach to the treatment regimen is needed [24].

Beginning with the year 2015, the National Institute for Clinical Excellence has published evidence-based information regarding the treatment of postmenopausal complaints and pathologies. The management of these symptoms needs to be individualized, and should primarily aim to improve the patients' QoL, and respecting its preference for treatment [53]. So, an excellent clinician will be able to guide his patients towards most appropriate and effective treatment and to individualize it depending on the personal characteristics of the patients.

2. Objective

This paper aims to analyse the management strategies for menopausal symptoms, described in the literature. We also want to illustrate the main advantages and disadvantages of the therapeutic strategies addressed in the management of the pathologies specific to this biological period.

3. Material and Method

After a review of the last five years literature, we identified epidemiological studies, clinical cases, guidelines, and meta-analysis regarding the right management strategies for the symptoms and pathologies associated with menopause. Ninety-four articles initially selected were considered from databases (PubMed, Google Academic, and CrossRef) for this study, but only fifty-three fitted

the area of interest of this review, gathering recent statistics. Relevant articles were selected by using the MeSH keywords: menopause, vasomotor symptoms, hot flushes, migraine, genito-urinary syndrome.

4. Results and Discussion

4.1. The management of vasomotor disorders

VMS principally include nocturn sweats and hot flushes. According to various studies, approximately 50.3% of postmenopausal women report repetitive episodes of hot flushes [16] and 82.1% report night sweats [7]. Vasomotor disorders also include several symptoms, such as intense heat during the night, which may last between 5 and 10 minutes. These symptoms may also lead to mood and sleep disorders, requiring medical care [9].

Although the pathophysiology of these manifestations is still unclear, it appears that the changes in the endocrine system of women at post-reproductive age are the underlying cause of these disorders. The dramatic decrease in serum estrogen levels, the decrease of circulating serotonin, and the increase in norepinephrine, were incriminated as determinants of these vasomotor disorders [1]. During the reproductive period, estradiol (E2) represents the active form of estrogens. E2 is converted to estrone, which has a lower biological potential, thus explaining the involvement of these estrogens in the promotion of vascular disorders [1].

Currently, HRT or estrogen-progesterone therapy is the most useful tool used for relieving night sweats and hot flushes. A study by Botelho and co-authors, which included a cohort of 66 Brazilian women with vasomotor symptoms, followed the effects and safety of nanostructured transdermal patches of progesterone, estriol, and estradiol, over 60 months of the administration. According to the results published by the investigators, in 92.5% of cases was observed an improvement in vascular kinetic symptoms, when compared to baseline [11]. Typically, HRT may decrease hot flushes and sweats severity and frequency, with more than 70%, in about one month of continuous administration [2].

In the United States, the most commonly used forms of oral estrogen for VMS improvement are estradiol and conjugated estrogen. Standard doses of estradiol and conjugated equine estrogens are 1.0 mg and 0.625 mg [3], respectively. Estradiol-releasing transdermal patches are also available. They release between 0.0375 mg and 0.05 mg daily estradiol. Patches that release very low doses of estradiol, 0.025 mg or 0.014 mg daily [3] could also be administered.

Combined sublingual or topical preparations for hormone replacement therapy have also shown their effectiveness in relieving vasomotor disorders, according to a research of Ruiz and coworkers. To test the variability of these symptoms under treatment, 160 women received local bioadhesive estrogen, and 40 received sublingual bioidentical estrogen. 70% of the patients treated with sublingual estrogen also received a combination of estrogens, and 100% of them received progesterone. 43% of the patients treated with local estrogen, also received a combination of estrogens, and 99% received progestins. While a high rate of the patients treated

with sublingual estrogen pills noticed a significant decrease of the flushes (31%), night sweats (38%), anxiety (42%) and sleep disorders (33%), topic estrogen does not appear to improve symptoms so quickly as sublingual therapy does [46].

Non-hormonal pharmacological therapies for menopausal vasomotor disorders include selective SSRI, clonidine, and gabapentin [28]. Paroxetine is an SSRI, and it is the primary non-hormonal option accepted by FDA for VMS management. The dose of paroxetine used in order to reduce vasomotor symptoms is lower than the dose used for treating psychiatric disorders. The results of a study that included 102 women showed that paroxetine decreased the frequency of moderate to severe vasomotor disorders and also showed excellent tolerability. Also, the safety profile of paroxetine was comparable to that of placebo therapy [26].

Sleep disorders are usually shared among midlife women. Studies have shown that 7.5 mg of paroxetine/day, administered for the alleviation of vascular symptoms, also reduced the number of awakenings significantly during the night and prolonged the sleeping period [38].

Pinkerton and colleagues conducted a study which included 600 women with a minimum of seven episodes of hot flushes over a day. They received a gabapentin treatment for 24 weeks. After 4 and 12 weeks of treatment, respectively, they reported a decrease in the frequency and severity of hot flushes compared to controls [39]. Another study by Hayes et al. showed that 0.6-2.4 g of gabapentin per day, administered in divided doses, might be a good option for treating hot flushes in women with natural or surgical induced menopause, who refuse hormonal therapy or have a contraindication for its use [22].

A randomized clinical trial enrolled 102 breast cancer patients, under chronic treatment with Tamoxifen, who received daily, 75 mg of venlafaxine, 0.1 mg of clonidine or placebo, during 12 weeks. After the follow-up period, the intensity of hot flushes decreased in the study groups in comparison with placebo. Some statistically insignificant differences were also noted between the first two cohorts of patients. However, adverse effects occurred more frequently in the venlafaxine-treated group (nausea, constipation, food intolerance). Therefore, both clonidine and venlafaxine are two viable non-hormonal options that can be used to treat menopausal vasomotor disorders [10].

Phytoestrogens are compounds derived from plants and possess structural similarity to 17-beta-estradiol (E2). This similarity with estradiol, allows phytoestrogens to produce (anti) estrogenic effects through their binding to ER (estrogen receptors). Phytoestrogens can be used as therapeutic agents in a multitude of cases such as the management of VMS, but their efficacy is doubtful [44]. Most phytoestrogens are represented by soy extracts, red clover, and genistein. Red clover can reduce the number of hot flushes episodes, especially in women with more than five episodes per day. Red clover can also reduce the intensity of other complaints from this period, but future studies are necessary in order to confirm the current knowledge [21]. Lambert et al. suggested that red clover was more useful and also was superior to placebo in decreasing self-reported vasomotor disorders [30].

By comparing the efficacy of

phytoestrogens from isoflavones to that of gabapentin in the treatment of post-menopausal vasomotor disorders, studies have shown that their efficacy is almost the same. However, isoflavones generated a better response in patients who associated depressive disorders, and gabapentin was more effective for patients with associated sleep disorders [48].

Non-pharmacological therapies were also used to treat or relieve hot flushes, night sweats, anxiety, and other postmenopausal vasomotor symptoms. For some patients, stress relief therapy has proven efficacy. Also, traditional Chinese medicine based on medicinal herbs, acupuncture, and yoga has generated contradictory results. Either physical exercises, relaxation, and breathing exercises have no beneficial effect in reducing VMS. As regards the administration of black cohosh food supplements, they have obtained favourable results in the treatment of vasomotor disorders, but concerns about the hepatotoxicity generated by this plant prevent the widespread use of dietary supplements containing it [33].

4.2. The management of headache and the postmenopausal migraine syndrome

More and more menopausal women refer to a specialist for appropriate treatment in order to improve headache and migraines [31]. Natural menopause improves the severity and frequency of migraines, while surgically induced menopause, does not. A crossover study involving 268 migraineurs women showed an improvement of the symptomatology once with the onset of natural menopause [14].

In terms of treatment, it is still controversial, and hormonal therapy is not considered the gold-standard in headache and migraines during this period. A recent Cochrane report on long-term hormone replacement therapy effects concluded that "the long-term health effects have not been documented" [17].

In a prospective study involving 50 menopausal women with headache and migraine without aura, the subjects were randomized and received: 50 mcg of transdermal estradiol every 7 days for 28 days, plus 10 mg of medroxyprogesterone acetate from the 15^{th} day to the 28^{th} day or 0.625 mg of conjugated estrogen daily for 28 days, plus medroxyprogesterone acetate 10 mg/day from the 15^{th} day to the 28^{th} day. After six months of treatment, none of the groups reported any improvement in the frequency of symptomatology, but in the group with oral treatment, the migraine and headache rates were higher compared to the initial values, and the concomitant analgesic consumption was higher [35].

The FDA did not accept estrogen therapy for the alleviation of migraine and other types of headaches because of the high risk of stroke [23]. Also, the results of the Women's Health Initiative Trials contraindicate the use of estrogen replacement therapy for routine in most women [42]. A study conducted by Rossouw and coworkers [45] showed that women who initiated HRT closer to menopause usually tended to have a reduced risk for coronary heart disease in comparison with women who initiated HRT more distant from this period and tended to have an increased risk for coronary heart diseases. The outcomes for their analyses were coronary heart disease defined as silent myocardial infarction and nonfatal myocardial

infarction, stroke, breast cancer, endometrial cancer, hip fractures, colorectal cancer, pulmonary embolism, and death. These outcomes were used in order to monitor the long-term effects of HRT or HRT associated with medroxyprogesterone administration, in women with an intact uterus. The results indicated that the number of side effects increased with increasing age, but there was no statistically significant additional effect of HRT by age for any of the mentioned outcomes. There were no significant increases in risk due to HRT for any outcome at ages between 50 and 59 years, but an increased risk for cardiovascular events, stroke, and other events was recorded in some older age categories.

The Women's Health Initiative hormone therapy trials were designed to evaluate the benefits and risks of hormone therapy taken for chronic disease prevention. Hormone therapy consisted of conjugated equine estrogens and conjugated equine estrogens plus medroxyprogesterone acetate for women who did not undergone a hysterectomy. During the follow-up period, the investigators observed that cancer mortality rates (breast cancer and endometrial cancer) were similar between the intervention group and placebo group. Also, the hormone therapy was not associated with risk of all-cause mortality, during 18 years of follow-up [32].

The plants containing phytoestrogens traditionally used to relieve headache and migraine, may also be useful in the holistic treatment of menopause migraines. A randomized, placebo-controlled study, of Burke et al. [52] assessed the efficiency of a product containing combined phytoestrogens in the treatment of migraine. This product contained black cohosh, soy isoflavones, and dong quai, and it was administered to 49 migraineurs women during 24 weeks. The results indicated a significant decrease in the frequency of the attacks when compared to the placebo group. However, the mixture of all these compounds makes it impossible to recognize the effect of each compound separately, and their efficiency has not been demonstrated [12].

Kirichenko et al. administered a natural product, rich in natural phytoestrogens such as Vitis vinifera, green tea leaves (*Camellia Sinensis*), conifers powder (*Humulus Lupulus*) and garlic powder (*Allium Sativum*) to the patients included in their study cohort. After 24 months of follow-up, the results indicated a significant improvement in climacteric symptoms in both control and placebo groups [27].

Red clover is a dietary supplement used in the therapy of menopausal symptoms. It is also used for the maintenance or improvement of bone and cardiovascular health, with no adverse effects reported. Red clover was also used for the treatment of migraine syndrome, but the number of studies is limited, and further clinical trials are needed to confirm the usefulness of this dietary supplement.

Venlafaxine is a derivative of phenylethylamine, which blocks the presynaptic reabsorption of the serotonin (5-HT) and noradrenaline. Although it is predominantly used in the treatment of depression, Venlafaxine has proven its efficacy as a therapeutic agent for postmenopausal migraines and headache. In a prospective randomized, double-blind study, venlafaxine was efficient in 80% of cases who received 75 mg/day and in 88.2% of cases who received 150 mg daily [36].

In conclusion, postmenopausal headache is less common compared to headache or migraines occurring in younger age, but the management of these symptoms can be a real therapeutic challenge. Cardiovascular or other medical or psychiatric disorders could limit the therapeutical strategies of menopause symptoms. Since HRT often leads to the aggravation of migraines and involves an increased cardiovascular and stroke risk, an alternative therapeutic approach is recommended.

Other alternative options for treating migraine include acupuncture, yoga, and aerobics, but considering that the biological mechanisms of postmenopausal migraine are still to be discovered, all these methods are not recognized as therapeutic tools for menopause-associated headache. Also, further studies are needed to describe the pathophysiology and appropriate clinical behaviour for this condition.

4.3. The management of depression and cognitive disorders

In the elderly, depression represents a significant problem of public health, and a possible correlation between menopause and depression is of significant practical importance. Estrogen deficiency may increase the sensitivity to depression and estrogen therapy after menopause could improve mood and knowledge. However, the clinical relevance of estrogen administration is still controversial.

There is a series of data suggesting that estrogen replacement therapy might be considered for relieving mild symptoms of depression associated with hot flushes, sleep disorders, or other climacteric symptoms. However, there are no specific data from randomized trials indicating whether estrogen can be used as therapy for depressive disorders during the menopausal transition or in late menopause, but new findings suggest that estrogen might be useful as a complementary therapy, associated with inhibitory serotonin reuptake inhibitors [8].

The studies that evaluated the role of oral E2 in the therapy of menopausal depression have yielded controversial results. A study by Rasgon et al. included 16 women diagnosed with major depressive disorder, according to DSM-IV, who received estrogen replacement therapy, in order to see its effects on depression. Ten patients received only estrogen replacement therapy, while the remaining 6 received fluoxetine associated therapy. After the completion of the study, investigators suggested that estrogen replacement therapy could be used as a remedy for depression during menopause. Also, in cases with minimal response to the treatment with serotonin reuptake inhibitors, exogenous estrogen may have an additional beneficial effect [43].

E2 patches may be a more promising treatment for menopausal depression. Cohen et al. [13] concluded a 60% remittance rate among perimenopausal depression participants, while two clinical trials on the same subject showed remission of 68% and 80%, respectively, compared to 20% and 22% in the placebo groups [15], [47].

According to recent investigations, the effects of estrogen therapy for depression are distinct in perimenopause, when compared to the postmenopausal period. STAR * D study [5] included 896 premenopausal women and 544 postmenopausal women with depression, diagnosed according to DSM-IV criteria.

The patients received citalopram for a period of 12 to 14 weeks. 25% of the women received exogenous hormonal therapy, as follows: oral pills for premenopausal women and HRT for midlife women. Finally, differential effects were observed depending on the reproductive status of the women. The effect of citalopram was more pronounced in premenopausal women who took oral contraceptives, but it did not differ according to hormonal status in postmenopausal women. The results indicated that the utility of E2 as adjunctive therapy for SSRIs in pre- and perimenopausal women remains to be demonstrated, but it is not useful in postmenopausal women.

Another strategy to manage the depression associated with menopause is the administration of selective serotonin reuptake inhibitors (Escitalopram, Citalopram, Fluoxetine, Sertraline, etc.).

A study by Wroolie and colleagues followed the effects of Escitalopram on women aged 45-65 years, with depressive disorders. The treatment of postmenopausal depression with escitalopram proved its efficiency in mood and cognitive improvement. It can also maintain and improve the intricate attention and cognitive flexibility. However, escitalopram seems to aggravate the sound fluency of postmenopausal depressive women [54]. Therefore, this selective serotonin reuptake inhibitor is more effective for depression therapy when compared to estrogen replacement therapy, and also has a positive impact on other menopausal symptoms.

Citalopram could also be an adjunctive treatment for depressed subjects whose symptoms did not improve after E2 treatment. A study involving 12 symptomatic women treated with citalopram illustrated that 91.6% of patients underwent total remission. Also, the symptoms that persisted after an initial 4-week treatment with E2 alone (tension, anxiety, fatigue, and concentration difficulties) significantly improved [49].

Medicinal plants represent a rich source of biomolecules with therapeutic value that can also be used to treat anxiety and depression in menopause. Hidalgo and co-workers [25] performed a double-blind, randomized study, including two groups who received red clover and placebo, during 90 days period. According to the Kupperman score, the "depression" and "nervousness" scales of the patients revealed a considerable decrease in these scores when compared to placebo.

Another randomized clinical trial was conducted to test the usefulness of *Cimicifuga racemosa* (black cohosh) for depression and anxiety. The results indicated that black cohosh showed no efficiency as an anxiolytic product when compared to placebo [4].

Thus, while the black cohosh is an excellent tool for the therapy of vasomotor symptoms, less attention has been paid to its anxiolytic and antidepressant activity.

4.4. The management of genito-urinary syndrome and sexual disorders

The atrophy of vaginal mucosa is common in midlife women. In the last years, this condition is known as genitourinary syndrome. The massive impact of vaginal dryness on the couple relationship, on the quality of life, and the daily activities is often underestimated

and subtracted. Informing women about the importance of this symptom is an essential factor that encourages them to contact a specialized service in order to seek appropriate treatment [18].

Lubricants and moisturizers could be efficient in relieving the discomfort during sexual intercourse, in women with moderate forms of vulvovaginal atrophy, especially for those who can not use estrogen replacement therapy or who refuse it. Women should choose an optimal product, in terms of osmolality and pH, and that is similar to the natural vaginal environment. Currently, the use of lubricants and vaginal moisturizers is recommended, either alone or in combination with systemic or local estrogen replacement therapy [18].

The genitourinary syndrome is a new term used to define a condition known as atrophic vaginitis/urogenital atrophy/ vulvovaginal atrophy, induced by the drastic decrease of estrogen levels. This condition has genital, urological, and sexual implications, and usually affects over 50% of the menopausal women. Early detection, pharmacological treatment or non-pharmacological therapies (laser therapies, lubricants, homeopathic remedies, and lifestyle changes) are necessary not only to improve the life's quality but also to prevent the exacerbation of the symptoms [20].

Local estrogen therapy is considered first-line therapy because of its efficiency and lack of adverse effects. It is used for the treatment of moderate to severe symptoms. It works by restoring the premenopausal vaginal micro medium, by thickening the epithelium, increasing vaginal secretions, restoring the vaginal environment, and lowering vaginal pH. Overall, estrogen therapy can decrease uncomfortable vaginal dryness and relieve genito-urinary syndrome complaints [51].

Labrie et al. conducted a randomized, double-blind, placebo-controlled study to test the efficiency of daily intravaginal administration of 6.5mg DHEA versus placebo. During the follow-up period, the parabasal and superficial cells, vaginal pH, and the pain during intercourse were identified as symptoms of vulvovaginal atrophy. After the administration of 6.5 mg DHEA, intravaginal, for 12 weeks, the percentage of parabasal cells was lower when compared to placebo, while the percentage of superficial cells increased. The vaginal pH decreased in comparison with placebo, and dyspareunia decreased by 1.42 units compared to the baseline. The only side effect consisted of vaginal discharge due to DHEA melting at body temperature, and was reported by approximately 6% of women [29].

A study which included 302 postmenopausal women with moderate to severe vulvovaginal symptoms, compared the effects of vaginal tablets with estradiol associated with a vaginal moisturizer, to that of vaginal tablets associated with a placebo gel. According to the results of this study, estradiol vaginal tablets associated with a vaginal moisturizing cream do not offer any additional benefits compared to placebo-associated local estrogen in reducing postmenopausal vulvovaginal symptoms [34]. In order to prevent recurrent atrophy of the vagina and vulva, it is necessary to repeat the treatment with local estrogen [50].

Ospemifene is a non-hormonal drug approved by the FDA for the treatment of dyspareunia caused by menopausal vulvovaginal atrophy [6]. After 4 to 12 weeks of treatment with 60 mg Ospemifene daily, it reduced the number

of parabasal cells and the vaginal pH, compared to placebo [6]. After 12 weeks of Ospemifene administration, more than 75% of women reported an improvement of at least 1 point of symptoms of vaginal atrophy and more than 80% of dyspareunia. Also, up to 46% and 53% of women, respectively, had an improvement of at least 2 points of the symptomatology [40, 41].

Regarding the vaginal lubricants, they may produce a temporary improvement of symptoms, such as mucosal dryness and dyspareunia. The benefits of vaginal moisturizing creams may last longer if they are continuously used, but their efficiency in the genito-urinary syndrome is lower than the local estrogens administration. Also, less than 50% of postmenopausal European women are satisfied with these products. The use of these products may be associated with vaginal irritation, contact dermatitis, and skin allergies [50].

Other products that have proven their efficacy in maintaining vaginal health include phytoestrogens, which are non-steroidal estrogen receptor binding compounds. These compounds may have some beneficial effects on the urogenital system. Given the lack of safety data for women with estrogen-sensitive tumours, phytoestrogens should be administered with caution in all cases [37].

Another strategy for vulvovaginal atrophy treatment consists of laser CO2 treatment. After the use of this therapy, beneficial effects, clinical improvement of symptoms, improvement in sexual life, and vaginal flora rehabilitation have been observed. So the CO2 laser is a non-pharmacologically tool used to treat postmenopausal vulvovaginal atrophy, but further research should be done in order to evaluate the long term effects of the laser procedure.

5. Conclusion

Vasomotor symptoms, genitourinary syndrome, sleep disturbances, sexual dysfunction, and mood disorders (depression and anxiety) are usually mentioned during the menopausal transition and in the postmenopausal period. The severity of the symptoms should guide therapeutic management. Estrogen replacement therapy is currently the most effective treatment for vasomotor symptoms and also improves the dryness of the vaginal mucosa. Therefore, hormone replacement therapy should not be prescribed as a chronic treatment. The genito-urinary syndrome complaints can be managed through local applications of estrogen. The dose, route of administration, and duration of hormonal treatment should be individualized according to the patient's symptomatology and status. For the majority of women aged 50-59 years old, with no associated comorbidities, the risks of substitution therapy are low.

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