

ADVANCEMENT OF THE FEMALE REPRODUCTIVE PHASES CORRELATED WITH POSTMENOPAUSAL COMPLICATIONS INTENSIFICATION: CURRENT APPROACHES TO THE PREVENTION AND TREATMENT

Abstract

Women go through menopause naturally as they age. Many women transition into menopause with few or no symptoms, while others experience severe or even incapacitating symptoms. When female gynaecologist Trotula of Salerno stated that "there are older women who put forth blood matter especially when menopause approaches them" in the 11th century, we had a very different notion of the menopause. However, little is understood regarding the effects of menopause on women's mental health, particularly in the case of severe and persistent conditions like schizophrenia. Many postmenopausal women get vulvovaginal atrophy, which is brought on by an inadequate oestrogen supply. Vaginal dryness, itching, irritation, and dyspareunia are symptoms. Oestrogen therapy was the usual for lowering bone loss when a link between menopause and osteoporosis was first recognised in the past, but there was little information on fracture prevention even though it was thought to be effective. Up until the Women's Health Initiative (WHI) research published data on 6 years of hormone therapy treatment in 2001, which showed an increase in heart attacks and breast cancer, this persisted. Patients were concerned and there was a significant decline in oestrogen use even though the hazards were minimal (1 per 1500 users annually). In further analyses, the WHI trial demonstrated that oestrogen in women between the ages of 50 and 60 really decreased fractures and averted heart attacks.

Keywords: Vulvovaginal atrophy, WHI, Dyspareunia, Vaginal dryness

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I. INTRODUCTION

1. **Menopause:** Nature's living things all have the potential to change. Today's blossom will wither tomorrow, and a leaf that appears green today will drop off. Humans also experience this. Humans go through a number of developmental or transitional turning points throughout their lifespan.

A girl's transitory changes begin when she reaches menarche. In this manner, a girl became a lady. The woman will eventually enter the stage of menopause, during which time she will experience a variety of physiological and psychological changes. However, the majority of women typically overlook these.

The phases of a woman's existence are structured around what Goddess Cultures referred to as the "blood mysteries": menarche (the first monthly flow of blood), delivery, which is accompanied by blood from birth. A woman may experience anovulatory cycles, which are menstrual cycles without ovulation, when her hormone balance starts to change. She might start to experience menopausal symptoms.

A persistent amenorrhea known as menopause results from the loss of ovarian activity. Menopause can only be diagnosed retroactively after a woman has experienced amenorrhea for a full year. Oestrogen-dependent tissue's function gradually declines as ovarian function declines. Menstruation and ovarian activity stop. As people age, the tissue in their vagina, vulvar, and other oestrogen-dependent organs such their breasts changes. In addition, fever follicles react to stimulate gonadotropins, which lowers the level of oestrogen and causes the symptoms of menopause.[1]

II. DEFINITIONS OF TERMS

Menopause: Menopause is defined as the permanent cessation of menstrual cycles, whether it happens spontaneously or is brought on by treatment such as surgery, chemotherapy, or radiation, by the World Health Organization and the Stages of Reproductive Aging Workshop Working Group [2].

Perimenopause: Perimenopause, menopausal transition, and early post menopause are the three stages of the perimenopause: normal menstrual cycles with fewer than 12 menstruations in the previous year, respectively (no menstruations during the past 12 months) [3-5].

Post menopause: The interval following the 12-month menstrual-bleeding break is known as postmenopause. Menopausal symptoms, including hot flashes, lessen or disappear during this phase. Cardiovascular disease and osteoporosis are more prevalent in postmenopausal women.

III. THE ENDOCRINOLOGY OF THE MENOPAUSE AND POSTMENOPAUSAL PERIOD

As a woman matures, her ovarian follicle count gradually declines. As granulosa cells are lost, the production of ovarian oestrogen and Inhibin declines. The FSH and LH levels are still high since the ovary is not providing any unfavourable feedback. Because the stromal compartment is spared, androgen synthesis from the ovary continues after menopause. Because of peripheral aromatization of ovarian and adrenal androgens, menopausal women continue to have low amounts of circulating estrogens. Since the principal site of aromatization is adipose tissue, obesity has an impact on numerous menopause side effects. According to theory, the thermoregulatory system resets and narrows in response to fluctuations in estrogens and FSH levels, this causes hot flashes. It is also believed that the emergence of these symptoms may be influenced by the lowered levels of serotonin and increased levels of norepinephrine [6, 7].

Markers of ovarian age include FSH, estradiol, inhibin B, and AMH, which are hormones of hypothalamic-pituitary-ovarian axis. The anterior pituitary gonadotrophs release FSH, which is controlled in part by inhibin B and estradiol through negative feedback, thereby making it a "indirect measure." Every menstrual cycle brings about changes in inhibin B and estradiol, which are reflected in changes in FSH levels. Higher early follicular FSH and enhanced FSH secretion are caused by higher early follicular inhibin B, which is diminished with ovarian ageing.

Since early ovarian follicles produce the glycoproteins inhibin B and AMH, these two markers directly reflect the ovarian follicular pool[9]. Inhibin B is largely released by preantral follicles, while AMH is primarily produced by primary, preantral, and antral follicles[10]. AMH levels stay constant throughout and between menstrual cycles because the majority of AMH is produced by gonadotropin-independent follicles. Both AMH and early follicular inhibin B levels fall as ovarian follicle count decreases with ageing. Granulosa cells in ovarian follicles respond to FSH stimulation by producing estradiol. Estradiol levels change as ovarian ageing progresses and finally fall in postmenopause. Studies on these hormones were conducted through the MT due to the significant alterations in these reproductive hormones brought on by ovarian ageing. Progesterone, luteinizing hormone (LH), inhibin A, and other reproductive hormones have also been studied in MT, but to a lesser extent. FSH, estradiol, inhibin B, and AMH are thus the main topics of this review[11, 12].

Table1: Summary of reproductive ageing hormones using STRAW criterion

Hormone	Peak Reproductive	Late Reproductive	Early MT	Late MT	FMP	Postmenopause
FSH (Follicle stimulating Hormone)	Normal	Increase	Increase	Increase		Increase
AMH (Anti mullerian hormone)	Normal/ Decreases	↓	↓	Undetectable		Undetectable
Inhibin	Normal	↓	↓	Undetectable		Undetectable
Estradiol	Normal	Normal	Normal	↓		↓

MT=Menopausal transition; FSH=Follicle stimulating Hormone; AMH= Anti-mullerian hormone; FMP=Final menstrual period; STRAW=Stages of Reproductive Aging Workshop

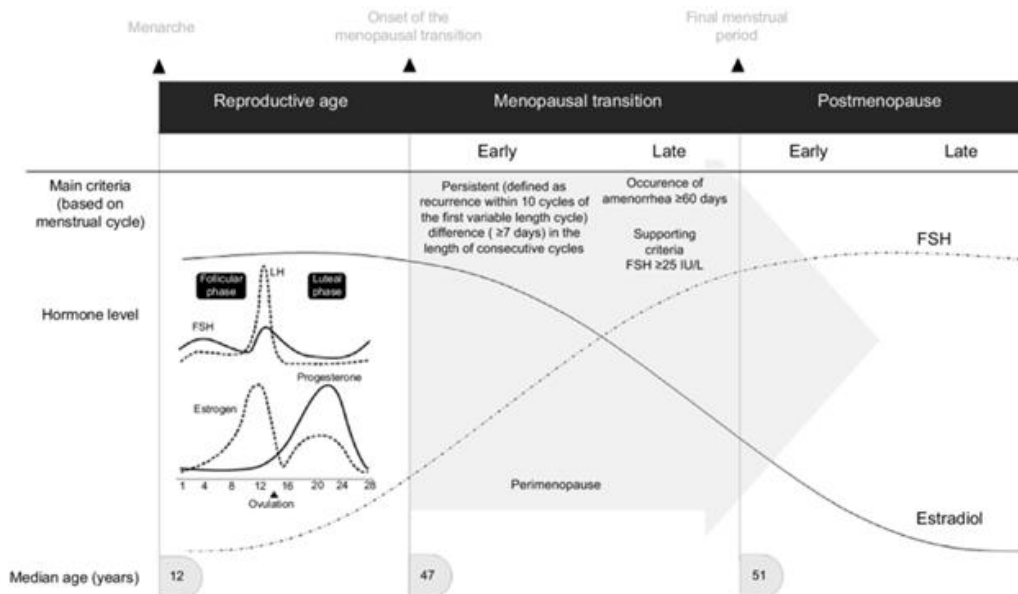


Figure 1: Progression through the Menopausal Transition and Postmenopause

IV. SYMPTOMS OF MENOPAUSE

Every year, 1.5 million women go through the menopause transition, which frequently brings on bothersome symptoms like vasomotor symptoms, vaginal dryness, decreased libido, insomnia, fatigue, and joint pain [13-15]. Because they feel that these symptoms are connected to the shifting hormonal milieu associated with menopause, the majority of women directly link menopause and the typical symptoms of hot flashes, vaginal dryness, and disrupted sleep (with or without associated night sweats).

Women may also experience cognitive impairments and depression symptoms during menopause, which have a more ambiguous and subtle hormonal connection. It can be difficult for women to deal with depression and cognitive decline, and the ageing female population's burden of illness is made worse. Since postmenopausal women are already at increased risk for osteoporosis and cardiovascular disease, it is crucial to address possibly reversible psychological conditions that could make treating medical conditions more challenging. For older female patients, patient care and health outcomes can be enhanced by having a better grasp of the risk factors, clinical presentation, and treatment options for these typical menopausal symptoms [16].

1. Vasomotor symptoms: Most women experience vasomotor symptoms throughout the menopausal transition, albeit each woman experiences these symptoms differently in terms of severity, frequency, and length. Up to 85% of menopausal women report having hot flashes [13]. Hot flashes can occur in up to 55% of women even before the monthly irregularity that marks the start of the menopausal transition begins, and they become more frequent and severe as women move through the menopause, peaking in the late transition and decreasing off over the following few years[14,17].

The precise reason for the hot flash has not yet been identified. The idea that is easiest to understand contends that changes in or a decrease in oestrogen production are associated with a resetting and narrowing of the thermoregulatory system. Although there is no immediate change in serum estradiol during a hot flash, it was often believed that hot flashes were primarily caused by an oestrogen withdrawal. Some people have linked hot flashes to varying levels of follicle-stimulating hormone (FSH) and estradiol[15]. The 5-HT_{2A} receptor in the hypothalamus is hypothesized to be unregulated by increased serotonin levels, which may be caused by decreasing oestrogen levels. The 5-HT_{2A} receptor may then become activated as a result of the increased serotonin that is subsequently produced. Hot flashes come from this activation, which modifies the set point temperature. Regardless of the precise cause of the hot flash, vasomotor symptoms can be reduced with the use of nonhormonal and hormone therapy[16,17].

2. Psychological symptoms: At least 20% of women experience severe menopausal transition symptoms. Women experiencing symptomatic menopausal transition have been found to have a higher prevalence of psychiatric symptoms, such as depression, anxiety, and sleep disturbance. It has not been possible to demonstrate a direct link between psychiatric problems and the symptomatic menopausal transition[19, 20].

Estrogens have an impact on the brain, affecting things like pain, movement coordination, and cognitive performance.

- **Schizophrenia:** The strongest sex hormone for women is 17-alpha oestradiol. Along with controlling primary and secondary sexual characteristics, it also has an impact on how the brain develops particularly the hippocampus and amygdala. Patients with schizophrenia also have issues with these brain regions. Additionally, it functions at other parts of the brain—particularly the basal forebrain, the hypothalamus, and the spinal cord—independent of receptors. Additionally, 17-alpha oestradiol has

neuroprotective qualities. Numerous 17-alpha oestradiol-regulated mechanisms may have an impact on how schizophrenia manifests [21].

- **Bipolar disorders:** The amygdala, hippocampus, cingulate cortex, locus ceruleus, midbrain raphe, and central grey matter of the brain, as well as other cognitive and mood-processing areas, have sex steroid receptors. In addition to the neuromodulators serotonin and norepinephrine, which are linked to the emergence of depression, estrogens, progestins, and androgens have an impact on a variety of neuromodulator processes [22]. Small or retrospective investigations of women with bipolar disorder during the menopausal transition have been conducted in the past. The majority included assessing mood retrospectively or cross-sectionally. According to bipolar illness research, the menopausal transition is associated with increased mood instability, specifically an increase in depression or a high rate of depression [23-24].
3. **Disturbances of sexuality:** The aetiology of sexual dysfunction does not correlate with hormonal changes, unlike hot flashes and Vulvovaginal atrophy. The diminished libido in postmenopausal women may also be brought on by vasomotor symptoms, sleep difficulties, and mood changes. [26]
 4. **Insomnia:** Sleep disturbances are a complex issue that becomes more prevalent throughout the menopausal transition. The major sleep issue is insomnia, which can also be secondary to other sleep disorders such obstructive sleep apnea (OSA) or restless legs syndrome, as well as hot flushes, mood disorders, psychological variables, and medical illnesses (RLS). Menopausal women who complain of persistent sleep disturbances should be referred to a sleep specialist for complete sleep treatment since undiagnosed and untreated. Sleep issues that are not treated can seriously harm one's health (27).
 5. **Vulvovaginal atrophy:** The symptoms of menopause that affect the Vulvovaginal area, such as Vulvovaginal dryness, recurrent UTIs, and dyspareunia, are less typically recognized by women (28). In order to alleviate the symptoms of estrogen insufficiency in women, menopausal hormone replacement therapy (MHT) has been regularly given for well over 50 years. For menopausal-onset vasomotor symptoms (VMS), such as hot flashes and night sweats, millions of women started MHT and continued it for a long time. In addition to alleviating vaginal symptoms such as dryness, irritation, itching, dyspareunia, and urine symptoms, hormone therapy was thought to have additional advantages such as protection from cardiac disease and osteoporosis. Atrophic vaginitis, an inflammatory response to atrophic alterations, is one of the symptoms of symptomatic VVA. Its intensity can range from unpleasant to incapacitating (29).



Figure 2: Symptoms of Menopause

V. DISORDERS RELATING FROM, OR POSSIBLY ACCELERATED BY THE MENOPAUSE

1. Osteoporosis

Introduction: Osteoporosis is characterized by decreasing bone density, which raises the risk of fracture. 52 percent of women over the age of 80 have osteoporotic fractures, with lower end radial fractures appearing around age 50 as the earliest warning sign, followed by vertebral fractures between ages 60 and 75 and hip fractures beginning in the late 70s, two thirds of the fractures happening after age 75. Age, gender, race (particularly Caucasians), genetics, reproductive status, inadequate calcium consumption, and exercise are only a few of the many variables that affect bone mass.[30] Dual energy absorptiometry (DXA) has replaced other methods as the industry standard, including densitometry of the radius, calcaneus, ultrasonography of the heel, radius, and phalanges, X-ray of the metacarpal and phalanges, and computerized tomography of the spine. The following diagnostic recommendations were made by the World Health Organization:

A standard T-score range is from +2.5 to 1.0.

Osteopenia is defined as a T score between 1.0 and 2.5.

T-scores of 2.5 or less indicate osteoporosis. [31]

- **Management of postmenopausal osteoporosis:** Depending on the assessment of the risk of fracture, both non-pharmacological and pharmaceutical therapies are advised. The FRAX system allows for risk stratification. Giving lifestyle recommendations and ensuring daily intake of the right amount of 800 IU of vitamin D and 1200 mg of total calcium. Medications are generally not required but may be used in cases of moderate risk outside dietary recommendations and acceptable daily consumption, be taken into account and vitamin D of calcium. High risk: In addition to lifestyle

recommendations, proper calcium and vitamin D intake, consider pharmaceutical treatment. Patients at increased risk include those who have hip or other fragility fractures.

- **Non pharmacological management:** Most of the post-menopausal women consume inadequate amounts of Calcium, Vitamin D and Protein which may increase the risk of fractures. To eradicate these symptoms 1200mg of calcium,800IU of Vitamin D and 1g of Protein given daily.[32,33,34]
- **Pharmacological management**

Table 2: Therapies for Osteoporosis

Name of the Drug	Points to consider	Dosing regimen
Alendronate oral (Fosamax)&Risedronate oral (Actonel)	Reduces the occurrence of Vertebral, vertebral and hip fractures	Alendronate 5 &10mg daily,35&70 mg Risedronate 5mg daily 35mg weekly and 150mg monthly
Ibandronate oral and IV	Prevent spinal fractures	2.5mg po daily,150mg P.O monthly,3mg IV/3 months
Zoledronic acid IV	Reduces the Occurrence of vertebral,Non vertebral and Hip fractures.High doses may cause Osteonecrosis.	5mg IV yearly
Raloxifene oral	Prevent Vertebral fractures,Beneficial in Patients who are intolerant to Biphosphate therapy	
Denosumab SC (Prolia)	Prevent Vertebral,Non vertebral and hip fractures	Denosumab 60mg for every 6 months
Teriparatide Sc(Forteo)	Prevent Vertebral,Non vertebral and hip fractures	
Calcitonin	Reduce incidence of Vertebral fractures	
HRT	Vertebral, hip, and non-vertebral fracture prevention in postmenopausal women is not advised for usage for this indication for the long term or for the primary purpose of OP prevention; weigh the advantages and dangers. is already being used to treat menopausal symptoms, may be suitable for OP prevention.	transdermal estradiol at a high dose of 2 mg. A moderate dose is 0.625 mg of conjugated estrogens. 1 mg of oral estradiol and 50 _g of transdermal estradiol minimal dosage: 0.3 mg of conjugated estrogens 25 _g of transdermal oestrogen in oral form at 0.5 mg

2. **Vasomotor symptoms:** The management strategy should be determined by the extent of the symptoms, the existence of other concurrent physical ailments, other menopausal symptoms, age, and the patient's personal preferences. Only a few heat flashes interventions are frequently successful in treating mild symptoms. To do this, reduce the temperature in the room, turn on fans, wear layers of heat-friendly clothes, and stay away from triggers (stress, spicy foods). Additional unproven advantages include weight loss,

stress reduction through mindfulness, cognitive behavioural therapy (CBT), acupuncture, hypnosis, yoga, and vitamin E.[36] Aside from behavioural and lifestyle adjustments, the majority of individuals with hot flashes ranging in severity require pharmaceutical treatment. Treatments using hormones and those without them are included. For women with no contraindications, hormonal therapy is the preferred form of treatment.

- **Harmonal therapy:** In Combination therapy, combining oestrogen and progestin is necessary for women with healthy uteruses to avoid uterine cancer, although oestrogen alone is sufficient for women who have had hysterectomy. Women with hypertriglyceridemia, migraine without aura, diabetes, hypertriglyceridemia, increased risk of venous thrombosis, gallbladder illness, and liver disease should choose transdermal therapy as their primary form of treatment. With oestrogen alone or in combination with progesterone, studies have shown that hot flashes are less severe and occur less frequently—by 87 percent in both cases.

Estrogen formulations come in the form of oral tablets, transdermal patches, topical gels, emulsions, and lotions. For vulvovaginal atrophy, lesser doses of intravaginal creams, pills, and vaginal rings are typically utilised; however, greater doses of vaginal rings are available for hormone replacement treatment (HRT).[37]

- **Non Hormonal therapy:** Lifestyle modifications, over-the-counter treatments, and prescription medications all fall under this category. Women over 60 or who have been postmenopausal for more than ten years are advised to use nonhormonal treatment. Other patient groups include symptomatic women with a history of MI, stroke, venous thromboembolic disease, estrogen-sensitive malignancies, those who are at higher risk of breast cancer, heart conditions, or venous thromboembolism, and people with diabetes (VTE) [38]. The benefits of black cohosh, ginseng, vitamin E, flaxseed, etc. have not been shown. SSRIs (paroxetine, escitalopram, fluoxetine, citalopram), SNRIs (venlafaxine, desvenlafaxine), clonidine (patch), and gabapentinoids are examples of nonhormonal pharmaceutical treatments that are successful (pregabalin, gabapentin). There is evidence that these can lessen both the intensity and frequency of hot flashes.[39]

3. Genito urinary syndrome

- **Hormonal therapy:** For moderate to severe symptoms, low dosage topical oestrogen is the preferred treatment. It enhances vaginal flora, secretion, hydration, and epithelial thickness. When use is stopped, the effect fades. However, it's interesting to observe that urine incontinence is not improved. In addition to increasing the patient's risk of breast cancer, heart disease, VTE, and cerebrovascular events, higher oestrogen doses do not appear to be more effective. There is no proof yet that these dangers are brought on by low-dose vaginal oestrogen. Progesterone is not necessary for endometrial protection with vaginal oestrogen, but any postmenopausal bleeding needs to be evaluated with endometrial biopsy and ultrasonography. Oncologists should be consulted when considering whether to suggest vaginal hormone therapy for breast cancer patients.[40]

- **Lubricants and moisturizers:** These are generally first-line treatments that can be used for milder symptoms, especially for female patients with estrogen-sensitive malignancies. These are sold over-the-counter as globules, creams, and liquids that act as vaginal lubricants and moisturisers. Hyaluronic acid, which is the active ingredient, helps to better hydrate the extracellular matrix. Studies have revealed that symptoms have improved both subjectively and objectively. Conjugated equine estrogens are administered daily (for two to three weeks, followed by one week off, repeat as necessary), as well as estradiol vaginal cream 0.01 percent (1 gm every two to three weeks), and estradiol rings (one every three months).
 - **Selective Estrogen receptor modulators:** Ospemifene, the first SERM licenced for patients with moderate to severe VVA symptoms who are not oestrogen candidates, is a selective oestrogen receptor modulator with affinity to vaginal mucosa. Since it increases the risk of venous thromboembolism (1.45/1000 women in the ospemifene group and 1.04/1000 women in the placebo group), it should not be used in women who have thromboembolic illness currently or in the past. A daily dose of 60 mg of ospemifene is administered orally.
 - Vaginal DHEA (prasterone), a therapy option for dyspareunia, is available. The daily vaginal suppository dose is 6.5 mg (0.5 percent formulation).
 - Laser therapy: Vulvovaginal atrophy has recently been treated with laser therapy. The objective is to promote fresh collagen production and collagen remodelling. Before advising their widespread use, more research is required to evaluate the procedures' long-term efficacy and safety.[40]
- 4. Sexual dysfunction:** Sexual dysfunction can have multiple causes. Sexual dysfunction has been shown to be improved by treating hot flashes, vaginal dryness, and mood swings. A lower amount of testosterone is thought to be responsible for some of the symptoms, particularly post-surgical menopause. In dyspareunia, DHEA and low-dose vaginal oestrogen can be administered. Testosterone therapy may help postmenopausal women's sexual function, including frequency and desire, according to a number of randomised, placebo-controlled scientific trials. It is necessary to discuss the potential benefits and risks as well as the scant information on long-term use. Additionally, before trying testosterone therapy, any less risky methods such as relationship counselling, sex therapy sessions, improving depression treatment, and treating another postmenopausal issue should be tried. For women, oral and transdermal medications are favoured.

Patients at risk for endometrial cancer, breast cancer, cardiovascular disease, or hepatic illness should use androgen with caution. Decreased HDL levels and hirsutism may result from it. Since testosterone is converted to oestrogen in the body, problems from oestrogen therapy must be closely monitored. Regular checks of the liver's function and lipid levels are also necessary.

- 5. Sleep disturbances:** The type of sleep disturbance the patient has might assist the clinician determine the best course of action. Once the precise cause has been determined, the proper course of treatment must be started. HRT should be used to treat insomnia

caused by vasomotor symptoms (VMS). Cognitive behavioural therapy works well for treating primary insomnia. Melatonin and non-benzodiazepine hypnotics are further options. Antidepressants may help with depression-related sleep problems. To detect and treat undiagnosed and untreated sleep disorders, women with recurrent sleep complaints should be referred to sleep specialists for comprehensive sleep management.

6. Psychological disturbances like schizophrenia and bipolar disorders

Harmonal therapy for Psychotic disorders: It has been successfully used to treat patients with schizophrenia who are on a regular drug regimen in addition to oestrogen and/or the SERM raloxifene. reduce both the positive and negative signs of psychosis. Various age groups of women. Depression is a common side effect for many psychotic women, particularly at menopause. The information on how HT affects mood is conflicting. While other trials revealed no effect, HT may elevate mood, according to a number of tiny short-term studies in middle-aged women with vasomotor symptoms. Some females may have mood impairment from the progestogens in HT, possibly those who have a history of premenstrual syndrome, premenstrual depressive disorder, or clinical depression. The effectiveness of HT in middle-aged or older women with depression has only been studied in a few number of randomised controlled trials (RCTs). Short-term estrogen's antidepressant effectiveness in depressed perimenopausal women is supported by two minor RCTs,

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