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RECENT ADVANCES

Menopausal Hormonal Therapy: Updates

Menopausal hormone therapy (MHT) is a general term that refers to both unopposed estrogen use in women who have had hysterectomies as well as combined estrogen-progestin therapy for women with an intact uterus.[1]

Menopause is the permanent cessation of the monthly menstruation cycle due to loss of ovarian follicular function and is deemed to have occurred after 12 consecutive months without menstruation. Generally, women reach natural menopause between the ages of 45 and 55 years. Menopause can occur earlier than 40 years in some women. This 'premature menopause' may result from various chromosomal defects, autoimmune diseases, or other unidentified reasons. Menopause can also be a consequence of different surgical procedures which involve the removal of ovaries or medical therapies that cause cessation of ovarian function like radiation therapy or chemotherapy.[2]

There is a marked decrease in ovarian estrogen production in menopause. This estrogen deficiency results in various menopausal symptoms like sleep disturbances, vasomotor symptoms (VMS; hot flashes, night sweats), sexual dysfunction, and genitourinary symptoms (e.g. Vulvovaginal atrophy, dyspareunia, increased urinary frequency).[1]

Menopausal symptoms usually start during the perimenopausal period, but can also start quite early like 10 years before the last menstrual period; and are associated with significant morbidity and adverse effects on quality of life.[3]

Though Women's Health Initiative (WHI) hormone clinical trials demonstrated an increased risk of coronary heart disease and stroke in women using MHT, based on other studies, the current guidelines have suggested that the benefits of HT typically outweigh the risks in case of most symptomatic women under 60 years of age and within 10 years of their final menstrual period when there are no contraindications.[4] Menopausal hormone therapy should hence be started around these time periods. In cases with premature ovarian insufficiency, hormone replacement should be continued up to the average age of menopause, irrespective of symptom load and absence of contraindications.[3]

MHT has been approved for four main indications in menopausal women:[5]

a. Vasomotor symptoms,
b. Prevention of bone loss,
c. Premature hypoestrogenism, and
d. Moderate to severe vulvovaginal symptoms.

Various different formulations, doses and routes of delivery are available for MHT. The choice should be based on the patient's individual characteristics and personal preferences.[5]

- Systemic estrogens are available in oral form, or as a transdermal patch, spray or gel; vaginal formulations exist in the form of creams, vaginal tablets or an insertable ring.
- For women without uterus, estrogen alone can be used. In women with intact uterus, a progesterone must also be used to protect against endometrial cancer.
- Low-dose vaginal estrogen therapy for genitourinary symptoms does not require progesterone.
- Progestins are available as both synthetic progestins and micronized progesterone, and come in the form of oral pills, transdermal systems (in combination with estrogen) and an intrauterine device.[5]

Advantages of MHT[3]

1. Improvement in vasomotor symptoms, sleep disturbances, genitourinary symptoms and mood disorders.

Table 1: Preparation of estrogens and progestin[5]

Preparations	Formulation	Route	Dose	Frequency
Transdermal estrogen dosing	17β-estradiol	Patch	0.025-0.1 mg	Twice weekly or weekly
		Gel	0.25 mg -1.25 mg	daily
		Spray	0.021/90 µL	daily
Oral estrogen dosing	17β-estradiol	Oral	0.5-2.0 mg	daily
	CEE		0.3-1.25 mg	daily
	CE		0.3-1.25 mg	daily
	Esterified estrogen		0.3-1.25 mg	daily
Low dose, local vaginal estrogen dosing for treatment of Genitourinary Syndrome of Menopause	17β-estradiol	Cream	1 g	Nightly for 2 weeks followed by twice weekly
		Tablet	10 µg	
		Ring*	2 mg	Replace every 90 days
		Insert	4 or 10 µg	Nightly for 2 weeks followed by twice weekly
	CE	Cream	0.5-2 g 0.5 g	Daily for 21 days, stop for 7 days and repeat Use twice weekly
Progestogen dosing	MP	Oral	100-300 mg	Daily
	MPA	Oral	2.5-10 mg	Daily
	Norethindrone	Oral	0.35 mg	Daily
	NETA	Oral	5 mg	Daily
	Megestrol acetate	Oral	20-40 mg	Daily
	Levonorgestrel	IUD	52 mg	5 years
Transdermal Combination Estrogen-progestogen dosing	17β-estradiol+ NETA		0.05 + 0.14 mg	Twice weekly
			0.05 + 0.25 mg	
	17β-estradiol + Levonorgestrel		0.045 + 0.015 mg	Once weekly
Oral estrogen-progestogen dosing (Cyclic/ Continuous)	CEE+MPA (Cyclic)	Oral	0.625 + 5 mg	CEE daily; MPA on days 15-28
	17β-estradiol +MP (Cyclic)		0.025-0.1 + 200 mg	17β-estradiol daily; MP for 10-14 days/month
	CEE+ MPA (Continuous)		0.625 + 2.5 mg	Daily
			0.625 + 5 mg	Daily
			0.3 + 1.5 mg	Daily
			0.45 + 1.5 mg	Daily
	Ethinyl estradiol+ NETA (Continuous)		0.0025 + 0.5 mg	Daily
			0.005 + 1 mg	Daily
	17β-estradiol + NETA (Continuous)		0.5 + 0.1 mg	Daily
			0.1 + 0.5 mg	Daily
	17β-estradiol+ MP (Continuous)		1 + 100 mg	Daily
	17β-estradiol+ Drospirenone (Continuous)		0.5 + 0.25 mg	Daily
			1 + 0.5 mg	Daily

CEE= conjugated equine estrogen; CE= synthetic conjugated estrogen; esterified estrogens are a specific plant-based formulation of synthetic estrogen. *This refers to rings which deliver local, low-dose estradiol.MP = micronized progesterone; MPA = medroxyprogesterone acetate; NETA=norethindrone acetate; IUD = intrauterine device;

2. Improvement in lipid and insulin sensitivity.
3. Reduction of the incidence of osteoporosis-related fracture.

Disadvantages of MHT[3]

1. Increased risk of breast cancer. Risk is much lower among people aged 50–59 years or among those who start treatment within the first 10 years of menopause.
2. Increased risk of ischemic stroke. It is primarily among older patients (aged >60 years) who start menopausal hormone therapy after 10 years following the onset of menopause.
3. Increased risk of venous thromboembolic events. This risk is lower with transdermal estrogen formulations compared with oral treatments.

Adverse effects[3]

Common adverse effects are vaginal bleeding, mastalgia and headache. Unexpected vaginal bleeding is the most common adverse event with MHT.

Contraindications[4]

Contraindications for HT are as follows:

- Women with a past history of coronary artery disease (CAD), stroke, myocardial infarction, unprovoked venous thromboembolism (VTE), or those who are at high risk for cardiovascular disease (CVD) should avoid HT.
- Unexplained vaginal bleeding should be evaluated prior to consideration of HT.
- Prior estrogen-sensitive cancers, such as breast cancer, systemic HT should be avoided.

The North American Menopause Society has recommended several nonhormone options for the treatment of vasomotor symptoms in women who are not good candidates for hormone therapy because of various contraindications: Cognitive-behavioral therapy, clinical hypnosis, selective serotonin reuptake inhibitors/ serotonin-norepinephrine reuptake inhibitors, gabapentin, fezolinetant; oxybutynin; neurokinin B antagonists; weight loss, stellate ganglion block.[3,6] Perimenopausal and menopausal symptoms can be significant negative effects on health as well as personal and professional lives of women. MHT is an effective management modality of menopause-associated VMS, whose benefits may outweigh the risks, especially in women within 10 years since menopause, less than 60 years old, and without significant cardiac diseases or contraindications to MHT.

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Author

Dr. Deepti Shrestha, Associate Professor
Department of Pharmacology, NMCTH

Chief Editor : Dr. Deepti Shrestha
Editors : Rudip Thapa, Rashmi Shakya Gurung, Dr. Lujaw Ratna Tuladhar, Dr. Rekha Paudel
Contact : Drug & Therapeutics Committee, NMCTH, Attarkhel **Email :** *dtc@nmcth.edu*
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DRUG SAFETY

Chelating Agents in Metal Intoxication: An Overview

Heavy metal toxicity is an uncommon diagnosis. Many of the elements that are considered as heavy metals have no known benefits for human physiology. Heavy metals such as lead, mercury, nickel, arsenic and cadmium are examples of such "toxic metals." Poisoning with heavy metals are usually related to occupational hazards. Human exposure to a number of metals such as lead, cadmium, mercury, manganese, aluminum, iron, copper, thallium, arsenic, chromium, nickel and platinum may lead to toxic effects, which are different for each metal. Some of the oldest diseases of humans can be traced to heavy metals associated with metal mining, refining and use. However, exposure to metals can occur through diet and medications as well.[1]

The Minimata Bay disaster is one such classic example of heavy metal toxicity due to environmental contamination. It was caused by the release of methylmercury in the industrial wastewater from a chemical factory in the city of Minamata, Japan. The incidence continued from 1932 to 1968.[2] Even with the present recognition of the hazards of heavy metals, the incidence of intoxication remains significant. Currently, millions of people living in and around Bangladesh are at risk for organ dysfunction and cancer due to chronic arsenic poisoning from the water supply.[3]

Heavy metals exert their toxic effects by combining with and inactivating the functional groups (-SH, -s-s, $-NH_2$, OH, $-PO_3$) of vital enzymes. They interfere with the normal physiological functions of these enzymes in the body leading to toxic effects. When intoxication occurs with such heavy metals, chelating agents are used. Chelating agents are heavy metal antagonists or the drugs that are used to prevent or reverse the toxic effects of a heavy metal on an enzyme. They form complexes with the heavy metal, rendering the metal unavailable for toxic interactions with the functional groups of enzymes thus accelerating the elimination of the metal from the body.[4]

The iron chelating agents currently in use include deferoxamine, deferasirox and deferiprone, all of which are highly specific for iron and have little or no effect on levels of copper, lead, calcium, magnesium or phosphate. Deferasirox and deferiprone can be administered orally, whereas deferoxamine requires parenteral administration.

The copper chelating agents in current use include penicillamine, trientine and dimercaprol. These agents are used largely to treat Wilson disease, the complications of which are caused by excessive body copper accumulation. Dimercaprol which is also known as British anti-Lewisite [BAL] is given intravenously. It is generally used only for acute or advanced symptomatic Wilson's disease. It is also effective in lowering levels of other heavy metals including arsenic and mercury. Penicillamine and trientine are orally available. These are the mainstays of prevention and therapy of Wilson disease. Trientine is generally better tolerated than penicillamine, which has many difficult side effects including acute liver injury. Nevertheless, penicillamine appears to be more effective in the initial management of symptomatic Wilson's disease and is preferred as a first line therapy.[5,6]

The lead chelating agents include succimer (dimercaptonol), dimercaprol (BAL), and ethylenediaminetetraacetic acid (EDTA). Succimer is orally available and appears to be more effective and better tolerated than the other therapies, which require intravenous administration. These agents are also used for arsenic, mercury and cadmium poisoning.[5]

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Author

Mrs. Rashmi Shakya Gurung, Assistant Professor
Department of Pharmacology, NMCTH