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Research Article

Do South Asian women with menopausal symptoms have access to optimal therapy?

Abhayaratna SA[1], Pinidiyapathirage J[2]

[1]Faculty of Medicine, University of Colombo, Sri Lanka.
[2]Griffith University, School of Medicine, Australia.

Abstract

Background

Menopausal symptoms can have a significant impact on a woman's quality of life. Information on availability of menopausal hormone therapy (MHT) in National Essential Medicines Lists (NEMLs) of South Asian (SA) countries has not been widely studied.

Objective

To review the availability of non-injectable MHT included in NEMLs of SA countries and to assess differences in availability compared to the recommended MHT preparations in the World Health Organization (WHO) model essential medicines list and the list of MHT available to women of a developed country in the Asia Pacific Region, while comparing with the healthcare expenditure and country's economic status.

Methods

Most recent NEMLs were obtained from all eight SA counties by visiting the Ministry of health/regulatory website of the respective country. Latest WHO model essential medicines list and Pharmaceuticals Benefits Scheme (PBS) schedule from Australia were obtained from the WHO and PBS websites respectively. Per capita health expenditure was obtained from The WHO Global Health Expenditure Database. Two investigators extracted the non-injectable MHT preparations independently from NEMLs and conducted the comparison.

Results

Except in two countries, in all other SA countries NEMLs were updated within the preceding five years. According to available data, seven SA countries had at least one separate preparation of oestrogen suitable for MHT while all countries had a separate progesterone preparation suitable for MHT. The oestrogen preparations available in the SA NEMLs were limited to either ethinyl estradiol or conjugated oestrogen tablets whilst in the WHO model, oestrogen preparations were not specified. In Australia, estradiol tablets were the only available oral oestrogen while there were four more different dosage forms of oestrogens available through the PBS Scheme. Progesterone preparations found in SA countries, WHO list and PBS schedule were similar, but oestrogen progesterone combination MHT preparations were only available in the PBS schedule. Per capita health expenditure was much higher in Australia compared to SA countries where a wide variation was observed.

Conclusions

The available evidence suggests that a larger population of SA women have access only to a very limited number of options if in need of MHT. In contrast, importance of MHT is highlighted in PBS Schedule. Although per capita health expenditure was low in SA countries, given that MHT products are relatively low cost and that there is a large proportion of women in menopausal age in this region, it would be imperative to update the WHO model list and NEMLs of SA countries to address the growing need of safe MHT and to improve the quality of life of postmenopausal women in our region.

Key words- Essential medicines, Menopause, Hormone therapy, South Asian countries

Background

Essential medicines, as defined by the World Health Organisation (WHO) are the medicines that "satisfy the priority health care needs of the population"[1]. WHO developed the first model essential medicines list in 1977 and it has been revised almost every two years thereafter. The most recent WHO model essential medicines list was devised in 2019 as the 21st version[2]. WHO promotes low and middle income countries to develop National Essential Medicine Lists (NEMLs) taking their own needs in to consideration. Many South Asian (SA) countries including Sri Lanka, has followed the WHO model list and formulated their own NEMLs which have been revised many times to reflect the changes in the country's needs with time. NEMLs help to make sure that cost effective vital medicines are available in sufficient quantities at all times and NEMLs are acknowledged by many as the list of medicines that should be given priority when making procurement decisions to make medicines available for a wider population at all times. Since large number of medicines in varying brand names have flooded the SA markets in recent times, having NEMLs give the governments of SA countries an opportunity to focus more on important medicines amidst a plethora of non-essential medicines in the market.

Similar to the WHO EML concept, PBS in Australia was initially developed to include only lifesaving and disease prevention medicines to be used in Australia. However the National Health Act No. 72 in 1959, introduced changes to the structure of PBS and the range of products included in the scheme was expanded in subsequent years[3]. The Pharmaceutical Benefits Advisory Committee makes recommendations to the Minister for health in Australia on the products to be included in the PBS general schedule and it is now updated on a monthly basis. New medicines are considered for inclusion in PBS schedule, if they are approved by the Therapeutic Goods Administration, proven to be effective, safe and following a cost effectiveness analysis[4]. The latest PBS schedule was released on 1st October 2020[5].

Menopause is the complete cessation of menstrual periods for a period of 12 months in a women of menopausal age group and this marks an important psychosocial change in women's life. With advances in health care in SA region, women living with menopause are increasing and in India alone it was estimated that 130 million women are expected to live beyond menopause by 2015[6]. Menopausal symptoms were found to be common among postmenopausal women and it has shown that menopausal symptoms reduce the quality of life, reduce the overall health status, increase irritability, depression and bone loss[7]. MHT completely resolve symptoms of menopause in around 80% of the treated women and reduce the severity of symptoms in others[8]. Although injectable MHT preparations are available, non-injectable MHT dosage forms are popular among menopausal women mainly due to convenience in administration. Following the safety concerns raised by the Woman's Health Initiative(WHI), a randomized controlled trial on MHT, there was a marked decline in the use of MHT due to perceived risks. However, subsequent studies have led to the consensus that risk benefit ratio is favourable when MHT is initiated in a postmenopausal women with symptoms, who are within 10 years of menopause and less than 60 years of age[9]. Worldwide, many professional associations now accept the importance of MHT and have issued guidelines on safe use of MHT in symptomatic postmenopausal women6,[10].

The aim of this article is to review the availability of safer MHT preparations, in different dosage forms in NEMLs in SA countries and to assess the room for improvement by comparing with a

medicine schedule of a developed country, whilst being mindful of the economic status and health-care expenditure in each country.

Methods

To download the latest available version of the WHO model essential list, we first searched the WHO essential medicines and health products web page. The latest version(21st list) was issued in 2019[2]. The same web page was searched to obtain information on all South Asian countries that have issued NEMLs. However, we found most of the NEMLs currently available in the WHO website to be old versions of the NEMLs of these countries. Therefore, we extended our search to the individual country's Ministry of Health and other health regulatory agency websites and obtained the latest version of the NEMLs for all South Asian counties. The PBS Australia web page was accessed to download the PBS General Pharmaceutical Schedule - Volume 1 which was effective from 1st October2020[5]. Country income status according to word bank classification was obtained from the world bank website and latest available per capita health expenditure for each country was obtained from the WHO Global Health Expenditure Database[11,12]. Two authors went through the NEMLs from the eight SA countries, WHO model EML, PBS schedule, country specific economic status and per capita health expenditure fact sheets and extracted the relevant data for each country to an Excel spreadsheet. Data sheets were compared for any omissions or errors in data extraction and thereafter the details were tabulated and comparisons made.

Results

All eight SA countries had NEMLs developed according to the format given in the WHO model essential medicine list. Six counties had their NEMLs revised within the last five years while in Sri Lanka and Afghanistan, latest available revisions were completed only in 2014. Most recently updated NEMLs were from Maldives and Pakistan (in 2018). Latest available WHO model essential medicines list was the 21st version issued in 2019 while PBS schedule was the most current, updated in October 2020. Summary of the NEMLs are given in **Table 1.**

Table 1: Year of publishing the EMLs in SA countries, WHO and Australia

Country	Year of latest version of NEML
Afghanistan	2014
Bangladesh	2016
Bhutan	2016
India	2015
Maldives	2018
Nepal	2016
Pakistan	2018
Sri Lanka	2014
WHO	2019
Australia*	2020

EML -Essential Medicines Lists, * Pharmaceutical Benefits Scheme schedule

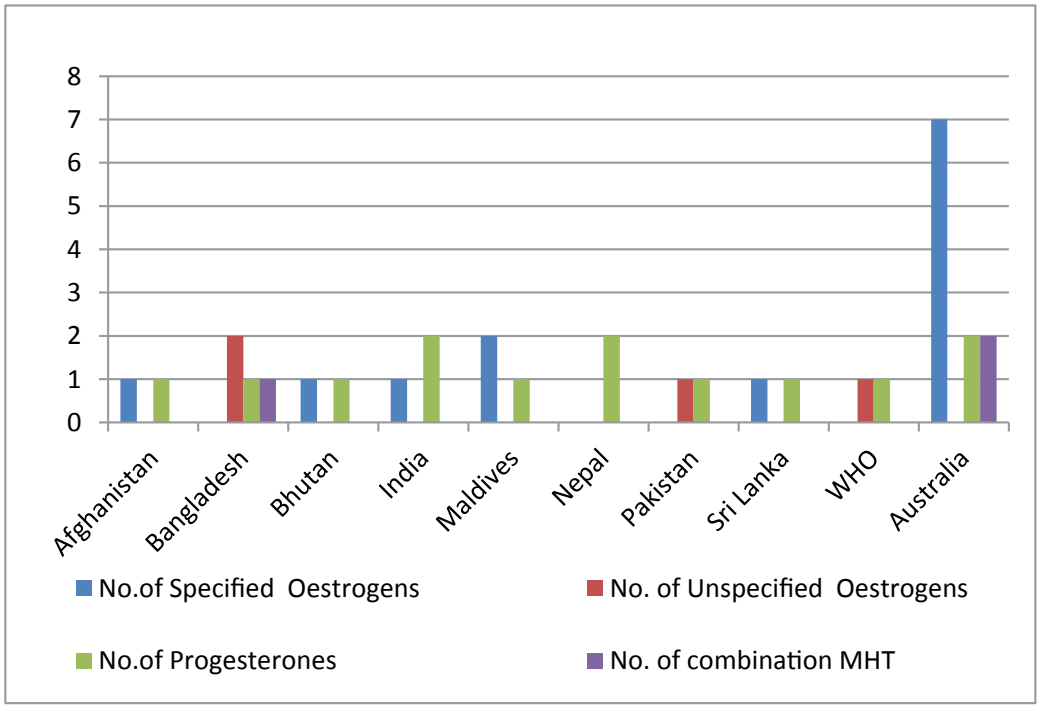
World Bank classifies countries into high income, upper middle income, lower middle income and low income based on per capita US $ income[11]. Afghanistan is the only low income country and Maldives is the only upper middle income country in SA region. All other SA countries belong to lower middle income status while Australia is a high income country. Latest available data on country specific annual per capita health expenditure in US $ was from the year 2017[12]. Among SA countries, the highest per capita health expenditure was seen in Maldives (US $ 1,006.94) followed by Sri Lanka (US $ 159.48). Per capita health expenditure in Australia (US $ 5,331.82) was nearly 80 times more than the average value for the SA region (US $ 64.47). Details of country classification by income and per capita health expenditure is summarised in the **Table 2.**

Table 2: Country specific income status and percapita healthcare expenditure

Country	2020-2021 World Bank country classification by income*	Per capita Health expenditure (US $) in 2017
Afghanistan	Low income	67.12
Bangladesh	Lower middle income	36.28
Bhutan	Lower middle income	96.80
India	Lower middle income	69.29
Maldives	Upper middle income	1006.94
Nepal	Lower middle income	47.92
Pakistan	Lower middle income	44.59
Sri Lanka	Lower middle income	159.48
Australia	High income	5,331.82

*Low income <US$ 1,036, Lower middle income US$1,036-4,045, US$ Upper-middle income 4,046 - 12,535, High income US$> 12,535

Figure 1: Oestrogen, progesterone and combination MHT preparations in NEMLs of each SA country in comparison to WHO EML and PBS schedule



In NEMLs of all SA countries and in WHO model essential medicines list, oestrogens and progesterones were listed as important categories of medicine but only in NEMLs of five countries a specific oestrogen preparation was listed. There were no combination oestrogen and progesterone MHT listed in NEMLs of SA counties or in WHO model list. PBS schedule had multiple oestrogen MHT products in different dosage forms. Country specific availability of MHT products are shown in **Figure 1.**

In Nepal, although ethinyl oestrogen tablets were available, tablet strength was too large to give the recommended dosage of 5 micrograms even after breaking the tablet in to a quarter. In all other countries recommended dosage could be reached by the available oestrogen tablet dose strength or by dividing the tablet into a half. Non oral dosage forms were only included in the NEML of Maldives (1 product) and in the PBS schedule (5 products). Summary of available oestrogen MHT in different countries is given in **Table 3.**

Table 3: Availability of different dosage forms of single oestrogen preparations in SA countries in comparison to WHO EML and PBS schedule

Country	Oral Oestrogen preparation in NEML/PBS	Lowest dose tablet	Suitability for MHT	Transdermal and topical oestrogen preparations in NEML/PBS	Strength of the preparation	Suitability for MHT
Afghanistan	Ethinyl estradiol	10 micg	Yes	None		
Bangladesh	Oestrogens with or without Progestogens for HRT *	-	-	None		
Bhutan	Ethinyl estradiol	50 micg	No**	None		
	Conjugated oestrogens	0.625 mg	Yes			
India	Ethinyl estradiol	10 micg	Yes	None		
Maldives	Ethinyl estradiol Oestrogen cream***	10 micg	Yes	None		
Nepal	Ethinyl estradiol	50 micg	No**	None		
Pakistan	Estrogens*	-	-	None		
Sri Lanka	Conjugated oestrogens	0.625 mg	Yes	None		
WHO	Estrogens*	-	-	None		
PBS Australia	Estradiol Estradiol valerate	2mg 1,2 mg,	Yes Yes	Estradiol pessary Estriol pressary Estradiol transdermal patch Estradiol gel sachets 0.1 % Estriol cream	10 micg 500micg 25,37.5,50,75 100micg/24hr 1mg 1mg/g	Yes Yes Yes Yes Yes

* Oestrogen preparation not specified
** Not suitable as the tablet couldn't be broken to get the recommended 5 micrograms dose
*** Strength of the oestrogen preparation not specified

Medroxyprogesterone acetate was the most commonly available progesterone preparation available for MHT in most counties. Few countries had norethisterone as the preferred progesterone preparation while some other countries had both products listed in their NEMLs. While most counties had the recommended dosage of 5 mg or lower dosage, only Bhutan had the 10 mg tablets which had to be taken as half the tablet if it is to be used to give the recommended dose in MHT. Different progesterone preparation in each country is shown in **Table 4.** When oestrogen and progesterone combination in a single preparation was considered, only the NEML of Bangladesh listed it as an essential item. However, a specific product(s) was not listed under this item. PBS schedule had one oral and one transdermal combination product available in different dosage strengths. The combination product availability details are given in **Table 5.**

Table 4: Availability of single progesterone preparations in SA countries in comparison to WHO model list and PBS schedule

Country	Oral progesterone preparation in NEML/PBS	Lowest dose tablet	Suitability for HRT
Afghanistan	Norethisterone	5mg	Yes
Bangladesh	Medroxyprogesterone acetate	5mg	-
Bhutan	Medroxyprogesterone acetate	10 mg	Yes**
India	Medroxyprogesterone acetate	5mg	Yes
	Norethisterone	5mg	
Maldives	Medroxyprogesterone acetate	2.5 mg	Yes
Nepal	Medroxyprogesterone acetate	5mg	Yes
	Norethisterone	5mg	Yes
Pakistan	Medroxyprogesterone acetate	5mg	Yes
Sri Lanka	Norethisterone	5 mg	Yes
WHO	Medroxyprogesterone acetate	5mg	Yes
PBS Australia	Medroxyprogesterone acetate	5mg	Yes
	Norethisterone	5mg	Yes

* Preparation not specified
** Suitable for MHT as half a tablet

Table 5: Availability of oestrogen progesterone combination preparations in SA countries in comparison to WHO EML and PBS

Country	Combined oral MHT preparations	Dosage	Combine transdermal MHT preparations	Dosage
Bangladesh	Oestrogen with progesterone*	-	None	
Other SA countries	None	-	None	None
WHO	None	-	None	
PBS Schedule	Estradiol + dydrogesterone	1mg+5mg 1mg+10mg 2mg+10mg	Estradiol + norethisterone patch	50micg+250micg/24 hr, 50micg+140micg/24 hr

*Preparation not specified

Discussion

Considering the aging population in South Asian region, it is expected that a larger proportion of women will live with menopausal symptoms in this region in the coming years. The benefits of MHT over the risks have been shown in menopausal women younger than 60 years of age[9]. Studies have also shown that Asian women reach menopause at an earlier age when compared to their counterparts in other regions in the world[13].

Although both combine oral contraceptive pills and MHT consist of oestrogen and progesterone, they are no interchangeable. Oral contraceptive pill has higher dosages of hormones to suppress the endogenous production and replaces them altogether, while lower dosages of oestrogens and progesterones are recommended for MHT. Patients with genitourinary syndrome of menopause benefit from topical MHT as they lack adverse effects of systemic treatment. Transdermal oestrogen preparations have shown to have a lower risk of strokes and venous thromboembolism (VTE) when compared with the systemic oestrogen therapy[14]. In certain high risk patients for VTE, transdermal oestrogen preparations would be the only suitable choice for MHT. Our analysis showed that only one SA country had topical oestrogen preparation while no SA country had transdermal preparation. Both dosage forms were available as multiple products in PBS schedule in Australia. Lack of inclusion of other dosage forms of oestrogen other than tablets in NEMLs of SA countries would have been due to high cost involved and due to the lower number expected to be on these dosage forms.

Commonly used oestrogen preparations in MHT include estradiol, conjugated equine estrogens (CEE) and ethinyl estradiol. Some studies have shown that oral CEE has 2-fold higher risk of venous thromboembolism when compared with oral estradiol[15]. Higher doses of ethinyl estradiol is used in oral contraceptive pill but as it is very much more potent than other oestrogen preparations and it could have higher rate of adverse events related to oestrogens. Therefore only dosages lower than 5 micrograms are recommended to be used in MHT[6]. The most preferred oestrogen preparation, estradiol, was only available in the PBS schedule but not in any NEMLs of SA countries. This was also not included in the WHO model list. In Bhutan and Nepal, the available ethinyl oestrogen tablet strength was not suitable to be used to provide the recommended lower dose in MHT. The difference in oestrogen type seen in NEMLs of SA countries and PBS schedule again may be due to the higher cost of estradiol compared to ethinyl estradiol as well as vast differences in economic status and health expenditure. In contrast to PBS schedule updated in 2020, countries with most updated NEMLs, they were revised in 2018 and some NEMLs were revised in 2014. Therefore, data on safety of estradiol over other preparations may not have been available at the time these NEMLs were revised.

While Australia is a high income country, six of the SA countries are in lower middle income category[11]. This difference is reflected conspicuously when per capita health expenditure of these counties were examined. Wide variation in per capita health expenditure was seen even between SA countries. Countries with relatively smaller populations like Maldives, Bhutan and Sri Lanka managed to spend more on health compared to countries with larger populations in SA. Although a huge gap was seen in per capita health expenditure between Australia and SA countries in general, most of oestrogen and progesterone preparations are not considered as high cost medicines.

Menopausal symptoms have shown to reduce the quality of life and cause significant economic burden to postmenopausal women and MHT has shown to considerably improve most menopausal symptoms[8,16]. Additionally, if we consider the population of women who would benefit from MHT, it may be appropriate to consider inclusion of safer MHT preparations in different dosage forms in WHO and NEMLs of SA countries. This will give the prescribers in SA region a better opportunity to effectively manage women with menopausal symptoms, raise their quality of life and yield economic benefits to women in our re-

gion without exposing them to excessive health risks.

Conflicts of interests - none

References

1. Essential medicines. Geneva: World Health Organization, 2019. Available from: http://www.who.int/medicines/services/essmedicines_def/en/ [Accessed on 4th Oct 2020]

2. National Essential Medicines Lists (NEMLs) Repository. Geneva: World Health Organization.2017. Available from: http://apps.who.int/medicinedocs/static/ Public-Subcollections/National-Essential-Medicines-Lists-NEMLs-repository/index.html [Accessed on 4th October 2020]

3. Goddard M. How the Pharmaceutical Benefits Scheme began. The Medical Journal of Australia. 2014; 201(1):S23-25

4. PBAC Guidelines Version 5, September 2016. Available from https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf. [Accessed on 20th October 2020]

5. The pharmaceutical benefits scheme 2020. Available from https://www.pbs.gov.au/ publication/schedule/2020/10/2020-10-01-general-schedule-volume-1.pdf, [Accessed on 20th October 2020]

6. Position Statement. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause 2017; 24:728-753

7. Sengupta A. The emergence of the menopause in India. Climacteric. 2003; 6:92–95

8. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Systemic Review 2004; CD002978. Available from https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002978.pub2/full

9. Stuenkel CA, Gass ML, Manson JE , et al. A decade after the women's health initiative–the experts do agree. The Journal of Clinical Endocrinology and Metabolism 2012; 97:2617–2618

10. Chetkowski RJ, Meldrum DR, Steingold KA, et al. Biologic effects of transdermal estradiol. The New England Journal of Medicine 1986; 314:1615

11. The World Bank. World Bank Country and Lending Groups 2020. Available from https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. [Accessed on 28th October 2020]

12. World Health Organization Global Health Expenditure Database 2020. Available from https://apps.who.int/nha/database [Accessed 29th October 2020]

13. Palacios S, Henderson VW, Siseles N, Tan D, Villaseca P. Age of menopause and impact of climacteric symptoms by geographical region. Climacteric. 2010; 13(5):419-28

14. Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV, Santen RJ. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology and Metabolism. 2015; 100(11):3975-4011

15. Smith NL, Blondon M, Wiggins KL, et al. Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. JAMA Internal Medicine 2014; 174:25–31

16. Whiteley J, DiBonaventura Md, Wagner JS, Alvir J, Shah S. The impact of menopausal symptoms on quality of life, productivity, and economic outcomes. Jurnal of Women's Health (Larchmt). 2013; 22(11):983-90