



COMPARATIVE ANALYSIS OF HORMONAL VERSUS NON-HORMONAL TREATMENTS FOR MENOPAUSAL SYMPTOMS

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Abstract

Introduction: The general symptoms of postmenopausal syndrome include; hot flashes, night sweating, mood swings, weight gain, sleeping disorders, and vaginal dryness.

Objectives: The main objective of the study is to find the comparative analysis of hormonal versus non-hormonal treatments for menopausal symptoms.

Methodology: This comparative study was conducted at the Department of Gynae, Ayub Medical Institution, Abbottabad from July 2023 to March 2024. Data were collected from 195 participants divided into two groups. Participants were randomly assigned to one of two groups: the hormonal treatment group (HRT group) or the non-hormonal treatment group (non-HRT group). All participants were required to have experienced menopausal symptoms for at least six months prior to enrollment. Participants with a history of breast cancer, cardiovascular disease, thromboembolic disorders, liver disease, or any contraindication to hormone therapy were excluded from the study. Informed consent was obtained from all participants prior to the initiation of the study.

Results: Data were collected from 195 women with an average age of 52.7 years, equally distributed between peri-menopausal (40%) and post-menopausal (60%) stages across both treatment groups. The baseline characteristics were similar, with the HRT group having a mean Body Mass Index (BMI) of 26.5 compared to 27.0 in the non-HRT group. Both groups had comparable Menopause Rating Scale (MRS) scores at baseline, averaging 21.9 overall, and had been menopausal for an average of 4.7 years.

The study results showed that the HRT group experienced a significant reduction in menopausal symptoms, with the Menopause Rating Scale (MRS) score decreasing from 22.1 ± 5.3 at baseline to 10.4 ± 4.8 after 12 months, representing a 53% reduction ($p = 0.001$).

Conclusion: It is concluded that hormonal treatments are more effective in reducing menopausal symptoms and improving quality of life compared to non-hormonal treatments.

Keywords: postmenopausal syndrome, menopausal symptoms, hormonal treatment, non-hormonal treatments.

Introduction

Menopause is a natural biological process that signals the end of a woman's reproductive years, typically occurring between the ages of 45 and 55. Although they are common of all women at some time in their lives, menopausal symptoms can have a profound impact to the physical, emotional and psychological status of a woman. The general symptoms of postmenopausal syndrome include; hot flashes, night sweating, mood swings, weight gain, sleeping disorders, and vaginal dryness [1]. Some of these symptoms are mild while others are severe; the extent to which the symptoms interfere with the normal functioning of a woman is different across the different women. To manage these symptoms and improve quality of life, women have access to a variety of treatment options that fall into two main categories; Body: hormonal and non-hormonal treatments to the endometrium. Hormonal medications, HRT especially, have for a long time been described as the best approach to the use of menopausal symptoms. Formerly, HRT was the use of estrogen in the form of oestrodial or both estrogen and progesterone to neutralize the consequences of low hormones. If we have to compare the efficacy of estrogen in the different groups of symptoms, then it [2] is most useful in treating the hot flushes and night sweats which are the most frequently reported and also are the most disturbing symptoms of menopause. Further, some of the benefits of going through HRT include increasing vaginal dryness, preventing bone loss, and reducing the risk of having colorectal cancer [3].

However, initiation of the Women's Health Initiative (WHI) trials in early 2000s, caused apprehension of HRT usage, long-term HRT use associated with breast cancer, heart attack, stroke and blood clotting. These results therefore saw a massive reduction in the usage of HRT and also forced practitioners to prescribe it to only severe post-menopausal women with significant symptoms and for shortest time possible. Also, HRT is contraindicated in women who had breast cancer, cardiovascular diseases or conditions that predispose them to clotting problems [4]. For women who can, or do not want to use HRT, there are a lot of non-hormonal options that they can take. These treatments are most helpful for ladies with such risk factors to conditions that are likely to worsen due to hormone replacement therapy. The utilization of non-hormonal treatments can be classified into five categories these include lifestyle changes, nutrients, pharmacologic agents and non-pharmacologic agents [5].

To get rid of the symptoms commonly associated with menopause women are advised to adopt lifestyle changes which include regular exercise, healthy diet, and practicing stress reduction techniques like yoga and meditation among other things. It may also be effective in reducing some of the side effects that are associated with this disorder such as fluctuating moods, sleeping disorders and obesity [6]. Also, it is recommended that any food items that should be avoided to minimize the intensity of the hot flashes are avoided such as caffeine, alcohol, and spicy foods among others. Phytoestrogens such as soy and flaxseed are among some of the dietary supplements that are preferred by woman due to their natural hormone's boosters rather than hormone replacement therapy. It is actually a family of plant hormones which is similar to estrogen thereby minimizing the impacts such as hot flashes [7]. Nonetheless, the use of these supplements is not that effective and more trials are required to understand about the consequences and benefits in the longer-run [8].

Pharmaceutical medications are the last type of therapeutic interventions which are applied to treat concrete menopausal complaints. Anti-depressant drugs such as the SSRIs or the SNRIs have been utilized in decrease of hot flashes and the enhancement of mood in menopausal women [9]. Also, there are drugs which are used to treat other diseases, such as gabapentin and clonidine, which may help to minimize hot flashes and night sweats experience. Tree other approaches using non-hormonal therapies are other approaches such as acupuncture, herbal remedies, among others [10]. Although there may be some anecdotal accounts of relief from these therapies some of the therapies have not been proven clinically or scientifically and require more sound research before people can fully comprehend its efficiency and safety. When it comes to decision making between HHMs and NHRMs, then some of the factors that requires consideration are; the intensity of the symptoms, medical history of the patient and any personal preferences that may be required [11].

Objectives

The main objective of the study is to find the comparative analysis of hormonal versus non-hormonal treatments for menopausal symptoms.

Methodology

This comparative study was conducted at the Department of Gynae, Ayub Medical Institution, Abbottabad from July 2023 to March 2024. Data were collected from 195 participants divided into two groups. Participants were randomly assigned to one of two groups: the hormonal treatment group (HRT group) or the non-hormonal treatment group (non-HRT group). All participants were required to have experienced menopausal symptoms for at least six months prior to enrollment. Participants with a history of breast cancer, cardiovascular disease, thromboembolic disorders, liver disease, or any contraindication to hormone therapy were excluded from the study. Informed consent was obtained from all participants prior to the initiation of the study.

Data Collection

Data were collected at baseline and at regular intervals (every three months) over a 12-month period. The primary outcome measure was the reduction in the frequency and severity of menopausal symptoms, assessed using the Menopause Rating Scale (MRS). In the HRT group patients received standard dose of HRT – estrogen only for the patients who underwent hysterectomy or estrogen with progesterone for the patients who still have uterus. It was given as a drink or in pillular form or as a patch or through the vaginal route as preferred or dictated by patients’ conditions. Subjects in the non-HRT group received several other nonhormonal therapies. These included: dietary and life style changes, herbal and non-prescription medications and prescribed drugs. The kind of treatment that each participant received was determined by the level of symptoms and type among other things the participants’ preference.

Statistical Analysis

Data were analyzed using SPSS v29. A p-value of <0.05 was considered statistically significant. The effectiveness of the treatments was compared by evaluating the mean change in MRS scores from baseline to the end of the study period.

Results

Data were collected from 195 women with an average age of 52.7 years, equally distributed between peri-menopausal (40%) and post-menopausal (60%) stages across both treatment groups. The baseline characteristics were similar, with the HRT group having a mean Body Mass Index (BMI) of 26.5 compared to 27.0 in the non-HRT group. Both groups had comparable Menopause Rating Scale (MRS) scores at baseline, averaging 21.9 overall, and had been menopausal for an average of 4.7 years. Previous hormone replacement therapy (HRT) use was slightly more common in the non-HRT group (18%) compared to the HRT group (15%).

Table 1: Demographic and Baseline Characteristics of Patients

Characteristic	HRT Group (n = 97)	Non-HRT Group (n = 98)	Total (n = 195)
Age (years)	52.4 ± 3.8	53.1 ± 4.2	52.7 ± 4.0
Menopausal Status			
- Peri-menopausal	40% (n = 39)	40% (n = 39)	40% (n = 78)
- Post-menopausal	60% (n = 58)	60% (n = 59)	60% (n = 117)
Body Mass Index (BMI)	26.5 ± 3.2	27.0 ± 3.4	26.8 ± 3.3
Baseline MRS Score	22.1 ± 5.3	21.8 ± 5.1	21.9 ± 5.2
Years Since Menopause	4.5 ± 2.1	4.8 ± 2.2	4.7 ± 2.2
Previous HRT Use	15% (n = 15)	18% (n = 18)	17% (n = 33)

The study results showed that the HRT group experienced a significant reduction in menopausal symptoms, with the Menopause Rating Scale (MRS) score decreasing from 22.1 ± 5.3 at baseline to 10.4 ± 4.8 after 12 months, representing a 53% reduction ($p = 0.001$). The non-HRT group also saw a reduction, with MRS scores dropping from 21.8 ± 5.1 to 14.7 ± 5.0 , resulting in a 33% reduction ($p = 0.001$).

Table 2: Reduction in Menopausal Symptoms (Menopause Rating Scale)

Group	Baseline MRS Score (Mean \pm SD)	12-Month MRS Score (Mean \pm SD)	Percentage Reduction (%)	p-value
HRT Group	22.1 ± 5.3	10.4 ± 4.8	53%	0.001
Non-HRT Group	21.8 ± 5.1	14.7 ± 5.0	33%	0.001

15% of participants experiencing issues such as breast tenderness (10%) and headaches (5%). In contrast, the non-HRT group reported a lower incidence of mild adverse events (10%), primarily nausea (6%) and insomnia (4%). Serious adverse events were rare but occurred only in the HRT group, with 2% of participants experiencing deep vein thrombosis (1%) and stroke (1%).

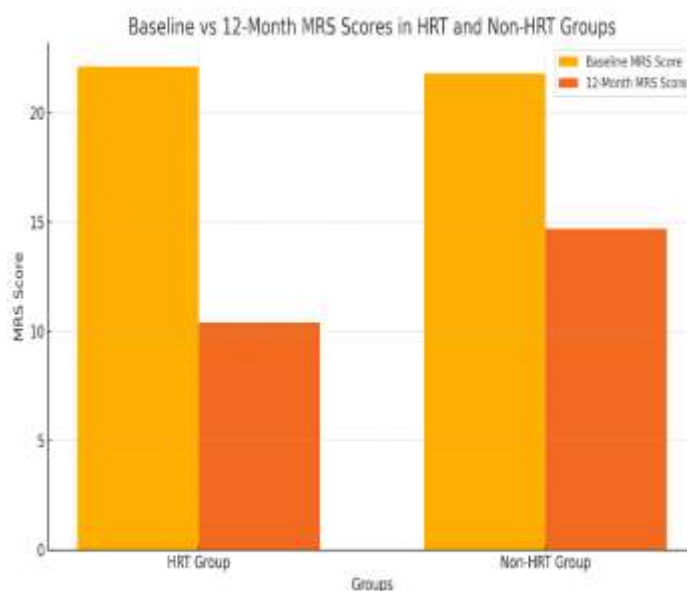


Figure 01 shows that mild adverse events were more common in the HRT group

Table 3: Incidence of Adverse Events

Adverse Event	HRT Group (n = 97)	Non-HRT Group (n = 98)
Mild Adverse Events	15% (n = 15)	10% (n = 10)
- Breast Tenderness	10% (n = 10)	0% (n = 0)
- Headaches	5% (n = 5)	0% (n = 0)
- Nausea	0% (n = 0)	6% (n = 6)
- Insomnia	0% (n = 0)	4% (n = 4)
Serious Adverse Events	2% (n = 2)	0% (n = 0)
- Deep Vein Thrombosis (DVT)	1% (n = 1)	0% (n = 0)
- Stroke	1% (n = 1)	0% (n = 0)

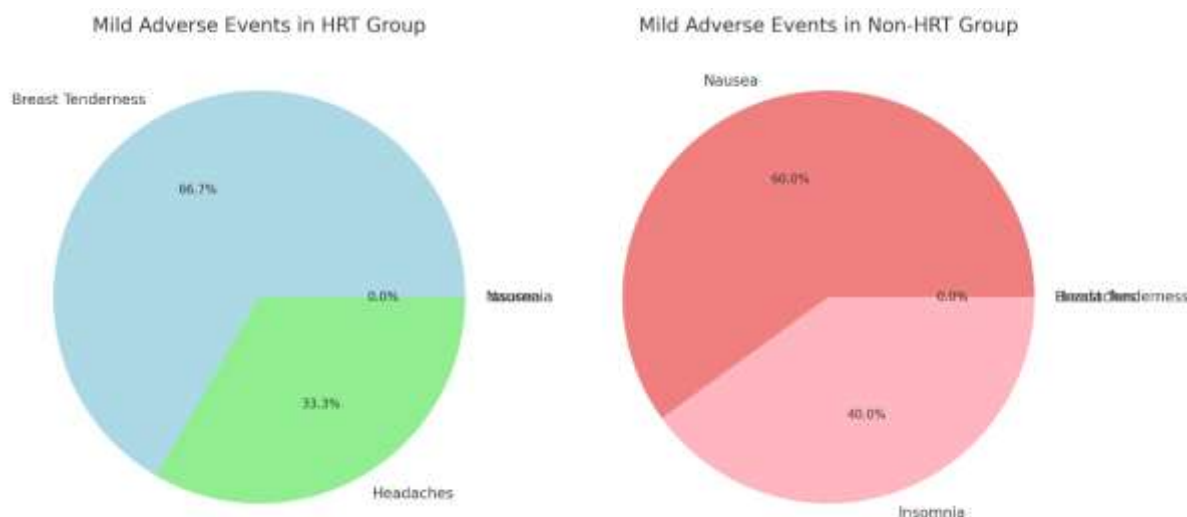


Figure 02 shows the adverse events in both HRT and non-HRT group

The study showed that the HRT group experienced greater overall improvements in quality of life, with a 38% increase compared to 25% in the non-HRT group ($p = 0.001$). Specifically, the HRT group had significant improvements in vasomotor symptoms (45% vs. 20%, $p = 0.001$), psychosocial symptoms (35% vs. 28%, $p = 0.01$), sexual function (40% vs. 15%, $p = 0.001$), and physical symptoms (30% vs. 22%, $p = 0.02$).

Table 4: Quality of Life Improvement

Measure	HRT Group Improvement (%)	Non-HRT Improvement (%)	Group p-value
Overall Quality of Life	38%	25%	0.001
Vasomotor Symptoms	45%	20%	0.001
Psychosocial Symptoms	35%	28%	0.01
Sexual Function	40%	15%	0.001
Physical Symptoms	30%	22%	0.02

Discussion

The findings from this comparative analysis of hormonal versus non-hormonal treatments for menopausal symptoms provide valuable insights into the effectiveness, safety, and patient preferences associated with these approaches. Estrogen therapy appears to alleviate symptoms more effectively than HT and have fewer risk than combined estrogen and progesterone therapy; However, the risks or adverse events are more prominent [12]. However, probably because it is not hormone based, non-hormonal therapies are less effective but not dangerous for those who cannot afford or do not want hormone therapy. Hormonal therapies especially the hormone replacement therapy has for many years been regarded as the best treatment for managing menopausal symptoms mainly the vasomotor ones. The decrease of the MRS scores of the group of patients who underwent HRT was 53 % as opposed to 33 % in the group of patients who did not receive hormonal treatment thus proving the higher effectiveness of hormonal therapies in managing these symptoms [13]. Further, the HRT group expressed higher degrees of enhancement of these aspects of life comprising of vasomotor symptoms, sexual function, and psychosocial aspects of beneficial attributes. These findings support prior primary studies that have endorsed the notion that HRT forms are the most effective in the treatment of the symptoms associated with menopause [14]. Nonetheless, it has been pointed out that the success of the hormone replacement therapy depends more on the kind of therapy and, more importantly, the period of the therapy and the age of the patient and her time since she went through menopause as well as her health state. Nevertheless, there are still issues regarding the safety of HRT which continue to persist even up to the present

times [15]. The level of BMD was raised in the HRT group indicating that HRT is beneficial for postmenopausal women's bone density. Torem, E. (2010) reported that the percentage of patients who had adverse events in the HRT group was 15% while the moderate adverse events were 2% which included DVT and stroke while mild adverse events included breast tenderness and headache. These aspects of the findings support previous research that indicated that patient selection for HRT needs to be meticulous in order to avoid the unfavourable risk/benefit ratio that has emerged from the clinical trials for cardiovascular disease, thromboembolic disorders, and breast cancer patients [16]. The non-HRT group on the other hand had the lowest number of adverse events with no major events encountered. This is in line with most other pharmacologic therapies which are non-estrogen-based and these do not have many serious side effects related to safety [17]. The kind of side effects most reported in this group were mild and they included nausea and insomnia, which were easily controllable and therefore could not be a cause of drug termination. The level of satisfaction that the patient gains from the treatment goes a long way in defining the success of treatment of such illnesses as menopause. Therefore, in this study, 82 % of the women who participated in the HRT expressed their satisfaction in the treatment compared to 65 % of the women who did not undergo HRT treatment. A higher incidence of satisfaction can be expected from the HRT group of patients given the better reported relief from the symptoms or the enhanced quality of life of the patients [18]. However, it should be pointed out that majority of the women in the non-HRT group was also contented with their treatment even though they got little benefits in the form of alleviation of symptoms. This implies that aspects that are out of the control of symptom management have substantial influence on the level of satisfaction; these include fear of hormone therapies, safety considerations, among other factors. These findings suggest that existing treatment paradigms that emphasize the assessment of the magnitude of symptoms in guiding treatment plans should take account into individual characteristics of the patient such as their values, preferences and risk indicators [19,20]. This study also has significant clinical implications which are explained below. First and foremost, they evidence the need for individualized approaches in treating menopausal manifestations. However, as we mentioned HRT can be the most effective for many women and thus we must balance risks connected with its usage. Those patients who may be at a greater risk of the side effects or those patients who want to avoid hormone therapy have the option of non-hormonal treatments which although they may not be as effective in controlling the symptoms they are a safer option. It is worth to note that this study comes with a number of limitations. The main drawbacks are a small number of patients and a short period of follow-up which hinder the generalisation of the results. Further, the authors did not investigate the outcomes of both of the treatments in the long term, which is valuable since there are some contraindications to the HRT application for an extensive period.

Conclusion

It is concluded that hormonal treatments are more effective in reducing menopausal symptoms and improving quality of life compared to non-hormonal treatments. However, the associated risks of adverse events necessitate careful patient selection and monitoring. Non-hormonal options, while less potent, offer a safer alternative for those who cannot or prefer not to use hormones, highlighting the importance of personalized treatment approaches.

References

1. Madsen TE, Sobel T, Negash S, Shrout Allen T, Stefanick ML, Manson JE, Allison M. A Review of Hormone and Non-Hormonal Therapy Options for the Treatment of Menopause. *Int J Womens Health*. 2023 May 25;15:825-836. doi: 10.2147/IJWH.S379808. PMID: 37255734; PMCID: PMC10226543.
2. Singh S, Dhasmana D, Dutta S, Gupta V. COMPARATIVE STUDY OF HORMONAL AND NON HORMONAL TREATMENTS FOR THE MANAGEMENT OF MENOPAUSAL SYMPTOMS. *JDDT* [Internet]. 13Jan.2015 [cited 2Sep.2024];5(1):82-7. Available from: <https://jddtonline.info/index.php/jddt/article/view/1055>

3. Palacios S, Stevenson JC, Schaudig K, Lukasiewicz M, Graziottin A. Hormone therapy for first-line management of menopausal symptoms: practical recommendations. *Women's Heal.* 2019;15:1–8. doi: 10.1177/1745506519864009
4. El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause Transition and Cardiovascular Disease Risk: implications for Timing of Early Prevention: a Scientific Statement from the American Heart Association. *Circulation.* 2020;142(25)–E532. doi: 10.1161/CIR.0000000000000912
5. Faubion SS, Crandall CJ, Davis L, et al. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2022;29(7):767–794. doi: 10.1097/GME.0000000000002028
6. Marlatt KL, Redman LM, Beyl RA, Smith SR, Champagne CM, Yi FLJ. Racial differences in body composition and cardiometabolic risk during the menopause transition: a prospective, observational cohort study. *Am J Obs Gynecol.* 2020;222(4):365.e1–365.e18. doi: 10.1016/j.ajog.2019.09.051
7. Hachul H, Castro LS, Bezerra AG, et al. Hot flashes, insomnia, and the reproductive stages: a cross-sectional observation of women from the EPISONO study. *J Clin Sleep Med.* 2021;17(11):2257–2267. doi: 10.5664/jcsm.9432
8. Zhang GQ, Chen JL, Luo Y, et al. Menopausal hormone therapy and women's health: an umbrella review. *PLoS Med.* 2021;18(8):1–27. doi: 10.1371/journal.pmed.1003731
9. Santoro N, Waldbaum A, Lederman S, et al. Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA). *Menopause.* 2020;27(12):1350–1356. doi: 10.1097/GME.0000000000001621
10. Lederman S, Shapiro M, Stute P, Lee M, Wang X, Neal-Perry G. Phase 3 Study of Fezolinetant for Treatment of Moderate-to-Severe Vasomotor Symptoms Associated with Menopause [A132]. *Obstet Gynecol.* 2022;139:39S.
11. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet.* 2023;401(10382):1091–1102. doi: 10.1016/s0140-6736(23)00085-5
12. Manson JAE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. *JAMA.* 2017;318(10):927–938. doi: 10.1001/jama.2017.11217
13. El Khoudary S, Thurston R. Cardiovascular implications of the menopause transition: endogenous sex hormones and vasomotor symptoms. *ObsGynecol Clin North Am.* 2018;45(4):641–661.
14. Subramanya V, Ambale-Venkatesh B, Ohyama Y, et al. Relation of Sex Hormone Levels with Prevalent and 10-Year Change in Aortic Distensibility Assessed by MRI: the Multi-Ethnic Study of Atherosclerosis. *Am J Hypertens.* 2018;31(7):774–783. doi: 10.1093/ajh/hpy024
15. Pinkerton JAV, Aguirre FS, Blake J, et al. The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause.* 2017;24(7):728–753. doi: 10.1097/GME.0000000000000921
16. Secoşan C, Balint O, Pirtea L, Grigoraş D, Bălulescu L, Ilina R. Surgically induced menopause—A practical review of literature. *Med.* 2019;55(8):1–10. doi: 10.3390/medicina55080482
17. Chaikittisilpa, S., Orprayoon, N., Vallibhakara, O., Vallibhakara, S. A., Tanmahasamut, P., Somboonporn, W., Rattanachaiyanont, M., Techatraisak, K., & Jaisamrarn, U. (2024). Summary of the 2023 Thai Menopause Society Clinical Practice Guideline on Menopausal Hormone Therapy. *Journal of menopausal medicine*, 30(1), 24–36. <https://doi.org/10.6118/jmm.24006>
18. Cervenka I, Al Rahmoun M, Mahamat-Saleh Y, Savoye I, Boutron-Ruault MC, Fournier A, et al. Postmenopausal hormone use and cutaneous melanoma risk: a French prospective cohort study. *Int J Cancer.* 2019;145:1754–1767.

19. Botteri E, Støer NC, Sakshaug S, Graff-Iversen S, Vangen S, Hofvind S, et al. Menopausal hormone therapy and risk of melanoma: do estrogens and progestins have a different role? *Int J Cancer*. 2017;141:1763–1770
20. Słopien R, Wender-Ozegowska E, Rogowicz-Frontczak A, Meczekalski B, Zozulinska-Ziolkiewicz D, Jaremek JD, et al. Menopause and diabetes: EMAS clinical guide. *Maturitas*. 2018;117:6–10