

The Beneficial and Adverse Effects of Raloxifene in Menopausal Women: A Mini Review

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Objectives: The present mini review aimed to summarize the existing knowledge regarding the beneficial and adverse effects of raloxifene in menopausal women.

Methods: This study is a review of relevant publications about the effects of raloxifene on sleep disorder, depression, venous thromboembolism, the plasma concentration of lipoprotein, breast cancer, and cognitive function among menopausal women.

Results: Raloxifene showed no significant effect on depression and sleep disorder. Verbal memory improved with administration of 60 mg/day of raloxifene while a mild cognitive impairment risk reduction by 33% was observed with administration of 120 mg/day of raloxifene. Raloxifene was associated with a 50% decrease in the need for prolapse surgery. The result of a meta-analysis showed a significant decline in the plasma concentration of lipoprotein in the raloxifene group compared to placebo (standardized mean difference, -0.43; 10 trials). A network meta-analysis showed that raloxifene significantly decreased the risk of breast cancer (relative risk, 0.572; 95% confidence interval, 0.327-0.881; $P = 0.01$). In terms of adverse effects of raloxifene, the odds ratio (OR) was observed to be 1.54 ($P = 0.006$), indicating 54% increase in the risk of deep vein thrombosis (DVT) while the OR for pulmonary embolism (PE) was 1.05, suggesting a 91% increase in the risk of PE alone ($P = 0.03$).

Conclusions: Raloxifene had no significant effect on depression and sleep disorder but decreased the concentration of lipoprotein. Raloxifene administration was associated with an increased risk of DVT and PE and a decreased risk of breast cancer and pelvic organ prolapse in postmenopausal women. (**J Menopausal Med 2018;24:183-187**)

Key Words: Depression · Lipoproteins · Raloxifene hydrochloride · Sleep wake disorders · Venous thromboembolism

Introduction

Menopause is a period in the life cycle of all women and is associated with hormonal changes,^{1,2} that presents with different symptoms, including hot flashes, night sweat, vaginal atrophy, stress, apprehension and decreased libido.³ Hormone replacement therapy (HRT) is a widely used therapeutic approaches to deal with menopausal symptoms.⁴

Based on the report by the Women's Health Initiative (WHI) the risk of cardiovascular events and breast cancer increase following the HRT regimen.⁵ These serious complication have resulted in reduced desire to use HRT for menopausal women.⁵

Lack of tissue specificity and distribution of estrogen-related complications within the body, have encouraged the researchers to think about medications with certain estrogen

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receptor modulating effects like raloxifene.^{6,7} Raloxifene as a non-steroidal pentathiophene from the second generation of selective estrogen receptor modulators (SERMs) that acts as a non-hormonal agent binding to the estrogen receptor that present estrogenic impacts on bone and anti-estrogenic impacts on endometrial and breast tissues.^{8–12} It should be noted that raloxifene was found to have beneficial outcomes on the brain, liver, and kidneys, as well as cardiovascular and musculoskeletal systems.^{6,13}

According to a recent meta-analysis, tamoxifen can decrease the plasma lipoprotein concentration by 20%.¹⁴ Daily administration of raloxifene at a dose of 120 mg has led to 33% reduction in the risk of mild cognition impairment.⁶ According to the result of a network meta-analysis, raloxifene significantly decreased the risk of breast cancer.¹⁵ Based on another meta-analysis, the use of raloxifene resulted in a 50% decrease in the need for prolapse surgery during 3 years follow up.¹⁶ On the other hand, some adverse effect such as deep vein thrombosis (DVT) risk and pulmonary edema (PE) was caused by raloxifene.¹⁷

Accordingly, it can be claimed that a review of efficacy and complications of taking raloxifene is necessary regarding the extensive and increasing use of raloxifene among menopausal women. Hence, we decided to conduct the current review to summarize the available literature on the advantages and disadvantages of raloxifene in attenuating the menopausal symptoms.

Materials and Methods

This study is a review of relevant publications about the effects of raloxifene on sleep disorder, depression and venous thromboembolism, plasma concentration of lipoprotein and cancer, breast cancer and cognition function among menopausal women.

Results

This mini review assessed the beneficial and adverse effects of raloxifene in menopausal women. Five studies included in this review (Table 1). These studies assessed the

effect of raloxifene on sleep disorder, depression, venous thromboembolism, pelvic organ prolapse (POP), plasma concentration of lipoprotein, Cognitive function and breast cancer.

1. Raloxifene and sleep disorder

A part of this systematic review focused on the effect of raloxifene on sleep disorder. Four out of 5 included trials in this systematic review assessed the effect of raloxifene on sleep disorder. Three studies failed to show any difference in efficacy between raloxifene and placebo on sleep disorder.⁶

2. Raloxifene and depression

This systematic review also focused on the effect of raloxifene on depression. Four out of 5 included trials in this systematic review assessed the effect of raloxifene on depression. Based on the findings of 1 study, raloxifene decreased the score of depression while 3 other studies did not find any beneficial effect for raloxifene in improving of depressive symptoms. Authors of the systematic review concluded that raloxifene had no beneficial effect on depression.⁶

3. Raloxifene and venous thromboembolism

Adomaityte et al.¹⁷ performed a meta-analysis to evaluate the effect of raloxifene on venous thromboembolism among postmenopausal women. Nine trials, involving 24,523 postmenopausal women with mean age of 59.4 years were included in their meta-analysis. Raloxifene was administered as a dose of 60 mg/day in most of the studies and the follow up period was 24 months. The odds ratio (OR) was 1.54 (95% confidence interval [CI], 1.13–2.11; $P = 0.006$), indicating 54% increase in the risk of DVT while the OR for PE was 1.05, suggesting 91% increase in risk of PE alone (95% CI, 1.05–3.47; $P = 0.03$).

4. Raloxifene and POP

A meta-analysis was performed to assess the adverse effects of raloxifene and found that treatment with raloxifene was associated with 50% decrease in the need for prolapse surgery during a 3 year follow up period.¹⁶

Table 1. Characterizes of 5 included studies in our review

References	Type of studies	Outcome	Type of intervention/control	No. of included studies/ No. of women	Conclusion
Mocellin et al. ¹⁵	A network meta-analysis	Cancer breast	Raloxifene/ Placebo	4 RCTs involving 37,336 postmenopausal women	The raloxifene decreased significantly risk of cancer breast (summary RR = 0.572). Incidence of severe adverse effects was lower in raloxifene compared to aromatase inhibitor (summary RR = 0.850).
Yang et al. ⁶	Systematic review	Cognitive function, depression, anxiety, and sleep disorder	Either 60 or 120 mg of raloxifene/ placebo	4 RCTs involving 6,140 postmenopausal women	Verbal memory improved after administration 60 mg/day raloxifene. The 120 mg/day of raloxifene decreased the risk of mild cognition impairment by 33%.
Ferretti et al. ¹⁴	A systematic review and meta-analysis	Lipoprotein	60 mg of used in all studies and dose of 120 and 150 mg were administered in some studies/ control group	7 clinical trial involving 771 cases and 607 for control group	A significant decline regarding plasma concentration of lipoprotein in raloxifene group compared to placebo (standardized mean difference = -0.43; 95% CI = -0.65 to 0.19; 10 trials).
Ismail et al. ¹⁶	Systematic review	The need for prolapse surgery	Raloxifene/ Placebo	3 trials and 1 meta-analysis	Treatment with raloxifene was associated with 50% decrease in the need for prolapse surgery for a 3 years period.
Adomaityte et al. ¹⁷	A meta-analysis	DVT	Different raloxifene/ Control	9 trials involving 24,523 postmenopausal women	OR was 1.54 (95% CI, 1.13-2.11; $P = 0.006$), indicating 54% increase in the risk of DVT while OR for PE was 1.05, suggesting 91% increase in risk of PE alone (95% CI, 1.05-3.47; $P = 0.03$).

DVT: deep venous thrombos, RCT: randomized controlled trial, RR: relative risk, CI: confidence interval, OR: odds ratio, PE: pulmonary embolism

5. Raloxifene and plasma concentration of lipoprotein

A meta-analysis was recently performed on the efficacy of raloxifene on plasma concentration of lipoproteins in postmenopausal women. The result of the meta-analysis showed a significant decline in plasma concentration of lipoproteins in raloxifene group compared to placebo (standardized mean difference [SMD], -0.43; 95% CI, -0.65 to 0.19; 10 trials). Subgroup analysis was performed based on dose and length of treatment. Subgroup analysis based on length of treatment revealed a better effect in studies administering raloxifene for less than 48 weeks compared to raloxifene administration for more than 48 weeks ($P = 0.001$). Publication bias was detected by Funnel plot. The result of meta-regression did not show any significant relation between plasma concentrations of lipoprotein with dose of raloxifene (slope of -0.001; $P = 0.801$). However, lipoprotein lowering

effect decreased significantly with the increase in the length of treatment (slope was 0.00 with only a slight asymmetry). Authors concluded that raloxifene can significantly improve plasma concentration of lipoprotein in postmenopausal women.¹⁴

6. Raloxifene and cognitive function

Verbal memory improved after daily administration of 60 mg raloxifene. Administration of 120 mg/day of raloxifene decreased the risk of mild cognition impairment by 33%. The authors suggested that it is difficult to draw a certain conclusion based on the current findings and that there is a need for larger studies and higher quality of life.⁶

7. Raloxifene on breast cancer

A network meta-analysis showed that raloxifene significantly decreased the risk of breast cancer (summary relative

risk [RR], 0.572; 95% CI, 0.327–0.881; $P = 0.01$). Furthermore, the incidence of severe adverse effects was lower in raloxifene compared to aromatase inhibitor (summary RR, 0.85; 95% CI, 0.76–0.95; $P = 0.04$).¹⁵

Discussion

This review aimed to summarize present knowledge regarding the beneficial and adverse effects of raloxifene in menopausal women. In this review, the effects of raloxifene on sleep disorder, depression and venous thromboembolism, along with plasma concentration of lipoprotein, breast cancer and cognition function were assessed in menopausal women. Raloxifene showed no significant effect on depression and sleep disorder. Raloxifene was associated with decreased risk of breast cancer and POP. However, raloxifene was associated with increased risk of DVT and PE.

Lipoprotein alone or in combination with other lipid or non-lipid risk factors may be involved in the increased risk of cardiovascular diseases (CVD).¹⁴ The postmenopausal women were reportedly shown to have low level of high-density lipoprotein (HDL) cholesterol and concurrently high levels of low-density lipoprotein cholesterol, triglycerides and cholesterol,¹⁸ indicating a probable reduction in the protective effect of HDL against CVD after menopause.¹⁹ Recently, a meta-analysis showed a 20% decrease in plasma lipoprotein in patients treated with tamoxifen. The effect of raloxifene on lipoprotein (a) is attributed to estrogen-like properties of raloxifene.¹⁴ Yang et al.⁶ found that raloxifene may act in a dose-dependent manner. They attributed this to the fact that raloxifene can easily cross the blood–brain barrier.

Adomaityte et al.¹⁷ concluded that raloxifene could lead to an increased risk of DVT and PE. However, their meta-analysis had several limitations, that made it difficult to draw a conclusion. First, a wide CI was identified in their meta-analysis, second, in all included studies, DVT or PE was assessed as the secondary outcome.¹⁴

Future studies should be conducted with a large enough sample size in order to enable researchers conduct subgroup analyses to compare the patients with elevated plasma lipoprotein concentrations and the patient with normal corresponding values. Additionally, the comparison between the

effects of raloxifene and other conventional medical therapies should be performed in future studies.

Conclusion

Raloxifene had no significant effect on depression and sleep disorder, but decrease the concentration of lipoprotein. Raloxifene was associated with an increased risk of DVT and PE and a decreased risk of breast cancer and POP in postmenopausal women.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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