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Mini Review

An Update on Therapy for Postmenopausal Symptoms with Emphasis on Selective Estrogen Receptors Modulators (SERM)-a Narrative Minireview

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Abstract

Treatment for problematic menopausal vasomotor symptoms as hormonal replacement' therapy has been debatable. Estrogen portrays a critical controlling hormone in the working the female reproductive system. Estrogen hormone controls a plethora of complicated physiological events. Possessing apart in reproduction, skeletal as well as cardiovascular system through actions on the two kinds of estrogen receptors-- estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) which portray unresearched transcription factors. Selective estrogen receptors modulators (SERM)are presently utilized for the treatment of bone elimination, breast cancer in addition to menopausal symptoms, metabolic along with neurodegenerative diseases; their properties which aids in their working in the form of agonist along with antagonist based on the target tissues. Tamoxifen: the first generation SERM utilization is in the form of adjuvant for the breast cancer having lesser risk in the premenstrual females as well as avoidance of breast cancer that is ER positive. Raloxifene: a second generation SERM portrays a significant for the treatment as well as avoidance of osteoporotic fractures in post menopausal women with avoidance of compression fractures of vertebral column. Innovative SERM molecules have become accessible, have corroborated they possess greater efficacy for the treatment of as well as avoidance of osteoporosis. They are inclusive of lasofoxifene, bazedoxifene, arzoxifene, along with ospemifene. Advantages of raloxifene vs bazedoxifene are getting evaluated. Although they possess therapeutic advantages and effects they do possess displayed inimical sequelae like venous thromboembolism (VTE). escalated endometrial cancer risk has been correlated with tamoxifen. Here we describe generation, invention and newer SERM's like lasofoxifene, bazedoxifene, arzoxifene, and ospemifene. Bazedoxifene might be used to avoid DM in menopausal ladies

Keywords: menopausal symptoms; hormonal replacement' therapy; Selective estrogen receptors modulators (SERM)

Introduction

Menopausal symptoms might be resulting in remarkable distress in addition to influence a woman's personal as well as social life. It is becoming greater apparent that in case left untreated in midlife these symptoms might result in changed quality of life, decreased work productivity as well as, plausibly totally change to dysfunctional health. To use or not to use Hormone therapy (HT) for the relieving menopausal symptoms has been the subject of considerable debate in the last twenty years. At the initiation beginning of the century, doubts crept in over the utilization of HT in view of botherations pertaining to cardiovascular in addition to cerebrovascular risks, as well as breast cancer, arising subsequent to the outcomes of a large randomized placebo-controlled trial. Observations of a sub-analysis of the trial data in addition to extended follow-up studies, as well as other more modern clinical trials in addition to observational studies, have yielded new corroboration on the actions of HT.

Genazzani., *et al.* [1], in 2021 updated how HT is an efficacious treatment for problematic menopausal vasomotor symptoms, genitourinary syndrome, as well as avoidance of osteoporotic fractures. Awareness has to be created in reference to a minimal escalated incidence amongst women of stroke risk having the tendency of continuing for years in addition to breast cancer risk with long-term estrogen-progestin utilization. Nevertheless, healthy women initiating HT immediately subsequent to the menopause would plausibly gain greater advantages in contrast to inimical sequelae from the treatment. HT possesses the capacity of improving problematic symptoms, throughout conferring offset advantages for instance decreased cardiovascular risk, an escalated bone mineral density in addition to a decreased bone fracture risk. Moreover, a reduction in colorectal cancer risk might be is obtained in women getting treated with estrogen-progestin therapy, and an overall but nonsignificant decrease in mortality has been found in women treated with conjugated equine lone estrogens or in combination with estrogen-progestin therapy. Where feasible, transdermal routes of HT delivery is preferrable in view of them possessing the minimal influence on coagulation. pertaining to combined treatment, natural progesterone is preferrable in view of it doesn't possess the antiapoptotic characteristics of other progestogens on breast cells. When initiating HT, utilization of lesser doses is needed in addition to escalated over a slow time period till efficacious regulation of symptoms is attained. Unless contraindications develop, patients might choose to persist with HT so long that the advantages are greater in contrast to the risks. Continued evaluation

of the woman's health status is warranted. Women with premature menopause who begin HT prior to 50 years of age apparently possess the max significant benefits with regards to longevity.

In women possessing problematic menopausal symptoms, HT has to be taken into account in the form of the mainstays of treatment. Clinical endocrinologists have to customize HT dependent on patient history, physical properties, as well as present health status so that that the advantages are greater in contrast to the risks [1].

Here we have attempted to update on the management of menopausal symptoms with the particular emphasis on Hormone therapy (HT) with the advent of newer SERM's.

Methods

Here we conducted a narrative minireview utilizing search engine pubmed, google scholar; web of science; Embase; Cochrane review library utilizing the MeSH terms like; post menopausal symptoms; hormonal replacement' therapy; selective estrogen receptor modulators; urogenital symptoms; vulvovaginal atrophy (VVC); osteoporosis; venous thromboembolism (VTE); fractures from 1995 till date in April 2024.

Results

We found a total of 300 articles out of which we selected 35 articles for this minireview. No meta-analysis was done.

Role of estrogen in menopausal symptoms

Considerable interest has been paid to the therapeutic application of estrogen as well as other hormones in reproductive endocrinology in the last 1-2 decades [2]. A plethora of hormonal alterations takes place once women are nearing menopausal status. The steep reduction in circulating quantities of 17betaestradiol in addition to estrone are the main of such changes. Progesterone quantities are escalated correlated with gonadotropins [follicle stimulating hormone (FSH) Luteinizing hormone (LH)] liberation from the anterior pituitary. Elimination of cyclicity in the menstrual cycle along with decline in estrogen quantities result in variable symptoms (inclusive of fluctuating mood, hot flushes, urogenital symptoms, vulvovaginal atrophy (VVC) as well as sleep aberrations) [3]. Long term elimination of estrogen has further been correlated with considerable chronic conditions - for instance, osteoporosis, coronary artery disease (CAD), alterations in lipidprofiles, diminished insulin sensitivity, Alzheimer's disease, dementia as well as breast cancer [4]. Since post-menopausal symptoms might impact quality of life (QOL), some clinicians are reluctant in initiating or continue to use in view of safety problems. Management of menopausal symptoms might be done using hormonal along with nonhormonal approaches [5]. Menopausal hormonal replacement' therapy (HRT) has been advocated for use in younger women possessing symptoms, being lesser than 60yrs of their last menstrual cycle period. These advocates have been described in guidelines in addition to continue to point that plausible benefits of hormonal therapy usually are greater than risks [6]. Epidemiological observational research studies considerably corroborate, steroid hormones particularly estrogen in post menopausal women for the prevention of long term illnesses in addition to short term tackling of symptoms for instance hot flushes. The long-term utilization of estrogen is associated with escalated incidence of complications like venous thromboembolism (VTE) as well as greater risk of endometrial cancer that might be avoided by addition of correct progesterone dosages in a woman possessing healthy uterus [2].

Estrogen receptor (ER)

Estrogen signaling portrays an elegant as well as key biological mode which control neural in addition to reproductive events as well as cardiovascular system. Estrogen influences cellular functions by cross talking with estrogen receptors, that might be existent in the nucleus or cytoplasm or plasma membrane (PM) [7]. Two kinds of estrogen isoforms- estrogen receptor alpha as well as estrogen receptor beta are existent with variety of organization fashion over tissues along with controlling of transcription [8]. A plethora of studies have illustrated that growth factors for instance - insulin like growth factor (IGF1), epidermal growth factors (EGF) along with other agents for instance dopamine as well as cAMP possess the capacity of facilitating ER actions as well as alter the agonist/antagonist balance of selective estrogen receptors modulators (SERM).An escalated protein kinase A (PKA) (a signal route action) particularly diminished the antagonistic potency of this along with other SERM's whereas escalating the agonistic effects of tamoxifen like anti estrogens [8]. Recognition has dawned regarding estrogen pharmacology is based on extra factors apart from ER in addition to coregulatory proteins along with gene promoter element (GPE). The ER 's possess the characteristics of binding with the DNA response elements (DRE) via direct crosstalk or intercommunicating, with extra transcription factors which bind DNA, thereby leading to crosstalk with the target genes. Taking into account all these factors, apparently different combined options for generating gene particular in addition to tissue controlling of SERM's [9]. The reduction in the quantities of estrogen or the elimination of in addition to its receptors are correlated with pathogenesis of different diseases malignancies (for instance- endometrial cancer, breast cancer, colon cancer, ovarian tumor, prostate cancer), neurodegenerative diseases (Alzheimer's disease [AD]; Parkinson's disease, dementia, Multiple Sclerosis (MS), stroke etc) osteoporosis, obesity, heart diseases. Estrogen 's have been therapeutically used in the form of HRT regarding menopause, contraception, in addition to infertility treatment [7].

Estrogen 's are necessary for growth, generation, cognition as well as skeletal sustenance along with other events [10]. It has been acknowledged that ER- ligand complex regulates gene transcription cross talking with the DRE. As per that it has been posited that specific structure of the receptor substrates complex impact unique subset of genes that are estrogen responsive, resulting in differential controlling, which ultimately leads to tissue selective sequelae [11]. In view of these crosstalk pathological disorders for instance cancers (endometrial cancer, breast cancer, colon cancer, ovarian tumor, prostate cancer), circulating along with metabolic conditions as well as cognitive conditions inclusive of, osteoporosis along with AD might take place. Estrogen use has been done with success in treatment of infertility, for menopausal HRT, in the form of Oral contraceptives [10].

Selective Estrogen Receptor modulators (SERM)

A broad variety of non Steroidal agents for instance SERM working in the form of agonists for certain target tissues in addition to antagonists for the other estrogen receptors (ER) [10,12].

Plausible advantages

Relief of Vasomotor Symptoms (VMS)

VMS or vasomotor instability alias hot flushes is one of the commonest symptoms which motivate women to initiate ERT.A hot flush portrays a considerable sensation of warmth which canonically gets initiated in the forehead, neck, chest top, however possesses the capacity of implicating the complete body. The time period of hot flush varies from 30-5'. Despite, its cause yield continues to be unresearched, changes in the hypothalamic thermoregulatory centre might be modes behind these events. Hot flushes might takes place in view of disturbance in the thermoregulatory centre caused reduction in estrogen quantities resulting in dilatation of vessels in addition to escalated sweating. Hot flushes might take place so uncommonly only twice a year or so commonly in the form of plethora of times/day. commonly taking place at night, these flushes might wake the women out of sleep, or might result in insomnia, fatigue, nausea, vomiting, night sweats, hidrosis, dizziness, headache, as well as palpitations for certain women. The best therapy diminishing menopausal vasomotor symptoms is ERT for a minimal 5 yrs time period followed by slow tapering of estrogen till vasomotor symptoms ebb [13].

Relieving Genitourinary along with Vaginal Atrophy (VA)

From the urogenital sinus originates the female reproductive system in addition to lower urinary tract; these organs possess an enrichment of ER's inclusive of bladder trigone, vagina as well as vestibule [14]. In the earlier life prior to menopause, greater quantities of estrogen ensure proper glycogen quantities in the vaginal epithelial tissue which aids in sustenance of healthy tissues amongst the vagina. The quantities of glycogen in the vaginal epithelium is key in generating an acidic milieu with a pH which fosters greater or lesser Lactobacilli. With the decline in estrogen quantities right through menopause their is thinning of the vaginal lining, that further becomes brittle, with the diminished glycogen quantities in the vaginal epithelial cells. An escalated probability of incidence of infections for instance bacterial vaginitis (BV) resulting in elevated pH quantities from acidic to alkaline. their is lesser elasticity of the epithelial layers of the vaginal epithelium possessing lesser vaginal lubrication. these alterations escalate the probability of vaginal dryness in addition to pain in post menopausal women at the time of sexual activity [15,16]. VA treatment is feasible by different non hormonal methodologies, nonprescription treatments inclusive of sexual activity, culmination of smoking, pelvic floor physiotherapy (PT) along with vaginal lubricants in addition to moisturizing creams [17]. Whereas local phytoestrogens apparently have a positive impact over VVA with improvement of maturation index, genital symptoms, vaginal pH quantities, morphology as well as activation of vaginal epithelium, in contrast to, oral phytoestrogens that are not efficacious. A plethora of menopausal symptoms inclusive of VVA get attenuated by HRT inclusive of estrogen-progestins, tibolone, Bazedoxifene or only estrogens in case of absence of uterus. The only SERM advocated for VVA treatment is Ospemifene. It possesses advantages actions over the epithelial cells of vagina, whereas minimal or no actions over actions over the other estrogen based organs. Pre Clinical-evaluation of has revealed that it possesses an anti estrogenic actions along with apparently possesses no inimical sequelae over the endometrial in addition to circulatory system [18].

Avoidance of osteoporosis

Numerous times utilization of HRT is done for continued time period for avoidance of complications for instance bone depletion as well as post menopausal fractures [15]. Diminished estrogen quantities are basically the single factor leading to pacey bone turnover, diminished bone mineral density (BMD), lesser bone strength, architecture breakdown with the higher probability of fragility fractures. Choice of the treatment has to be dependent over a correct balance amongst expenditure, risks in addition to effectiveness. In case of post menopausal women estrogen replacement' therapy (ERT) possess the capacity of sustenance of along with plausibly escalating BMD over all the bone localizations inclusive of femoral neck, lumbar spine in addition to forearm. Akin low dosage OC possess the capacity of countering the inimical sequelae correlated with hypoestrogenism in young women [19].

Avoidance of cardiovascular disease

The positive lipids controlling as well as the estrogen 's advantageous actions on the cells of the endothelium along with vasculature are implicated protection conferred by HRT over the cardiovascular well being [20]. The maximum cardiovascular disease (CVD) asssessment for each woman is assisted by taking into account genetic risks factors in addition to noncanonical risks factors faced at the time of her earlier life period. Transdermal MHT is the preferential treatment mode over the oral treatment for avoidance of probability of venous thromboembolism (VTE). observational research point that transdermal female hormones might be possessing a lesser risk of stroke in addition to VTE in contrast to oral estrogens, furthermore, they evoke lesser influence over the biological markers of inflammation in contrast to oral estrogens. Extra vigorous lifestyle advocates as well as treatment of simultaneous heart disease risks factors are needed in such plausibly high risk conditions [21].

SERM's portray unique agents which possess the capacity of management of osteoporosis in view of them working in the form of ER agonists in some target tissues. Nevertheless, they are further promising agents for avoidance of breast cancer due to their capacity working in the form of ER antagonist in the tissue of mammary gland, with particular influence on uterus along with vagina, which is dependent over the manner they crosstalk with the ER of these target organs. The ideal SERM's is being persistently looked for; that would be possessing estrogen like characteristics over the serum lipids in addition to bone, neutral actions over the womb along with an anti estrogenic actions over the breast tissues, however without any inimical sequelae correlated with the present treatments [22]. (Figure 1) [23] for the regions of actions of SERM's.

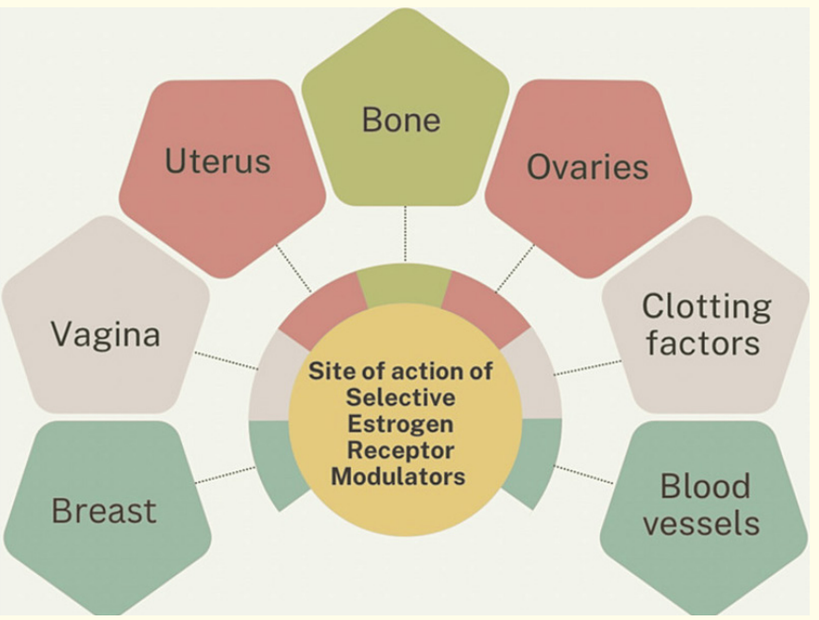

Figure 1: Courtesy ref no -23-Various sites of action of selective estrogen receptor modulators (SERMs).

Tamoxifen: first generation SERM

The trans isomer of a triphenylethylene substitute alias tamoxifen got initially isolated at the time of searching for anti fertility agents however was later illustrated to be possessing anti tumor probability. At presentist utilization is for the treatment of the breast cancer in its earlier stage along with on delivery with adjuvant Chemotherapy it possesses the capacity of escalating survival having minimal inimical sequelae seen [2,12]. there has been a reduction in the utilization of tamoxifen with the Selective estrogen receptor degraders getting invented for instance fulvestrant in addition to advantageous aromatase hampering agent, with its utilization in the form of adjuvant for the breast cancer having lesser risk in the premenstrual females as well as avoidance of breast cancer [24]. Lasofoxifene, bazedoxifene in addition to ospemifene portray newer SERM agents which have been evaluated for their plausible utilization in case of treatment as well as avoidance of osteoporosis. They are thought to be safe in addition to greater robustness in contrast to earlier SERM's [22].

Raloxifene: second generation SERM

Raloxifene represents a non steroidal SERM which is utilized for the treatment as well as avoidance of osteoporotic fractures subsequent to attaining menopause in addition to diminish the incidence of breast cancer in post menopausal women [25].

The effects over the variable tissues of the female body are

- **Over the uterus**- uterus represents a key organ pertaining to clinical safety concerns on continuous utilization of estrogenic agents in view of uterus possessing considerable sensitivity to estrogens. As per the uterine stimulation certain SERM 's vary from the canonical estrogens [3,11].
- **Over the blood vessels** - HRT escalates the probability of the VTE events 2 times. This is in combination with the risk factors for instance surgery, thrombophilia, greater body mass index (BMI) along with immobilization. VTE processes are commoner once utilization of Raloxifene is done [21].
- **Cognition**-it is biologically plausible that the avoidance of cognitive disturbances along with generation of the dementia syndromes for instance AD in post menopausal women by sustenance of the quantities of the estrogen high by utilization of combination estrogen –progesterone in the form of HRT. This actions gets apparently mediated by different pathways inclusive of dendritic sprouting, antioxidant actions as well as influencing variety of biochemicals implicated in cognitive working [26].

Newer SERM agents

- **Lasofoxifene-** Clinical studies have illustrated that lasofoxifene drastically escalated BMD in addition to diminished quantities of the bone turnover pointers in contrast to placebo. Furthermore, it is correlated with improvement of lipid profiles. Moreover, it has been illustrated that lasofoxifene diminishes the incidence of vertebral in addition to non vertebral column fractures in post menopausal women having osteoporosis as well as is correlated with a lesser generating breast cancer which is ER positive [27].

- **Bazedoxifene:** The maximum correct SERM regarding osteoporosis treatment as well as its avoidance is the one having agonistic actions over the bone, whereas not leading to activation of uterine or breast tissues. Apart from reducing bone elimination to the minimum, it would decline the incidence of breast soreness along with uterine

stimulation, reducing the risk of endometrial growth, polyp, hyperplasia, bleeding or endometrial cancer as well. It possesses advantageous actions in diminishing vaginal dryness in view of it possessing cycle agonistic actions over vaginal level. Moreover, it possesses attractive actions over the lipid metabolism along with vessels wall. In contrast to raloxifene, no vasomotor inimical sequelae was thought to be advantageous [28].

- **Arzoxifene:** in case of post menopausal women possessing lesser BMD or osteoporosis treatment with arzoxifene for 4 yrs drastically diminished the incidence of vertebral fractures in addition to invasive breast cancer. Nevertheless, the incidence of nonvertebral fractures wasnot decreased. Arzoxifene possesses no influence over CVD in post menopausal women having osteoporosis which is akin to that of raloxifene. Nevertheless, a greater incidence of VTE, endometrial hyperplasia, endometrial cancer, upper respiratory tract infections (URI), numerous pneumonia cases revealed, in addition to robust problematic processes of chronic obstructive pulmonary disease (COPD)were all correlated with treatment with arzoxifene [29].
- **Ospemifene:** The one in addition to only first non hormonal medicine that received FDA approval for the treatment of moderate to severe painful coitus taking in view of vulvar as well as vulvovaginal atrophy (VVA)alias atrophic vaginitis correlated with menopause. Ospemifene is the only SERM illustrating practically total estrogenic agonistic actions over the vaginal epithelial cells in addition to neutral to minimum estrogenic impact over the lining of the endometrium. Ospemifene illustrates its tissue particular influence over the breast, bone, uterus, coagulation markers along with serum lipid [30].

Role in metabolic control

Selective estrogen receptor modulators (SERMs) are a class of substances which crosstalk with estrogen receptors (ERs) as well as agonist or antagonist actions on ERs in a tissue-specific manner. Utilization of tamoxifen, a first generation SERM, is done for treatment of ER positive breast cancer. Utilization of raloxifene, a second generation SERM, was done for avoidance of postmenopausal osteoporosis. The third-generation SERM bazedoxifene (BZA) efficaciously avoids osteoporosis whereas avoiding estrogenic stimulation of breast in addition to uterus. Noticeably, BZA in combination with conjugated estrogens (CE) is a new menopausal treatment. The menopausal state escalates the susceptibility to metabolic syndrome (MetS) as well as type 2 diabetes (T2D, along with thereby the actions of SERMs on metabolic homeostasis are gaining interest. Thus Xu., *et al.* [32], summarized information regarding SERMs' influence on metabolic, homeostasis, obesity in addition to diabetes in rodent models as well as postmenopausal women (Figure 2-4). Thus BZA with (CE might aid in avoidance of MetS as well asT2D generation in postmenopausal women.

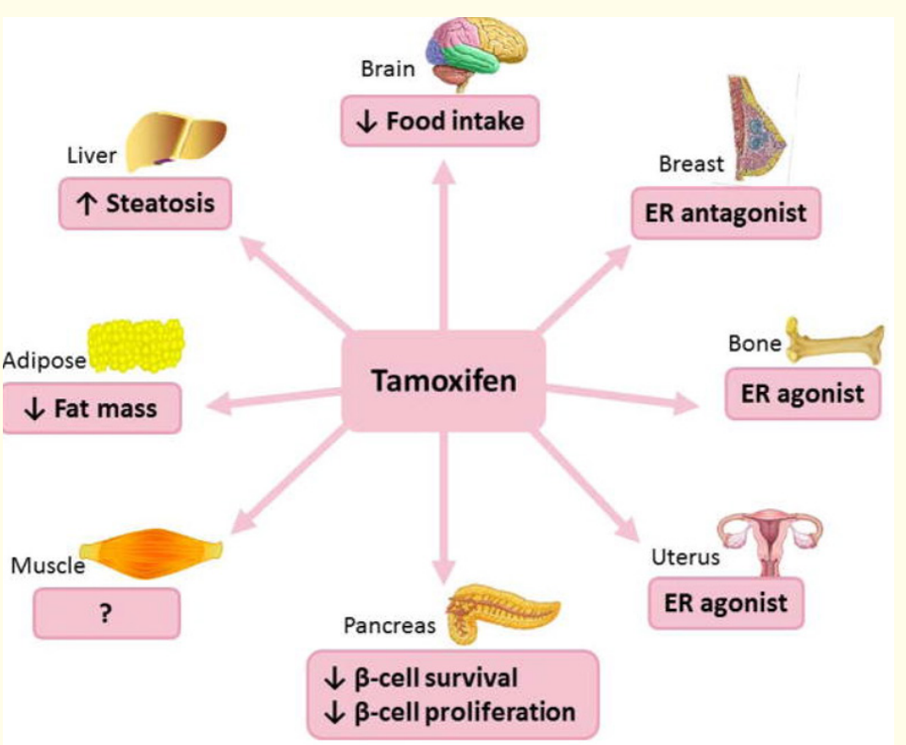

Figure 2: Summary of the effects of tamoxifen.

Courtesy ref no -31-Tamoxifen is an ER antagonist in breast and has estrogenic effects on bone and uterus. Tamoxifen decreases food intake, body weight and fat mass in rodents. It also lowers body weight in obese women. Tamoxifen decreases β-cell survival and proliferation in rodents and increases the incidence of diabetes in patients with breast cancer. Tamoxifen also promotes hepatic steatosis in rodents and women.

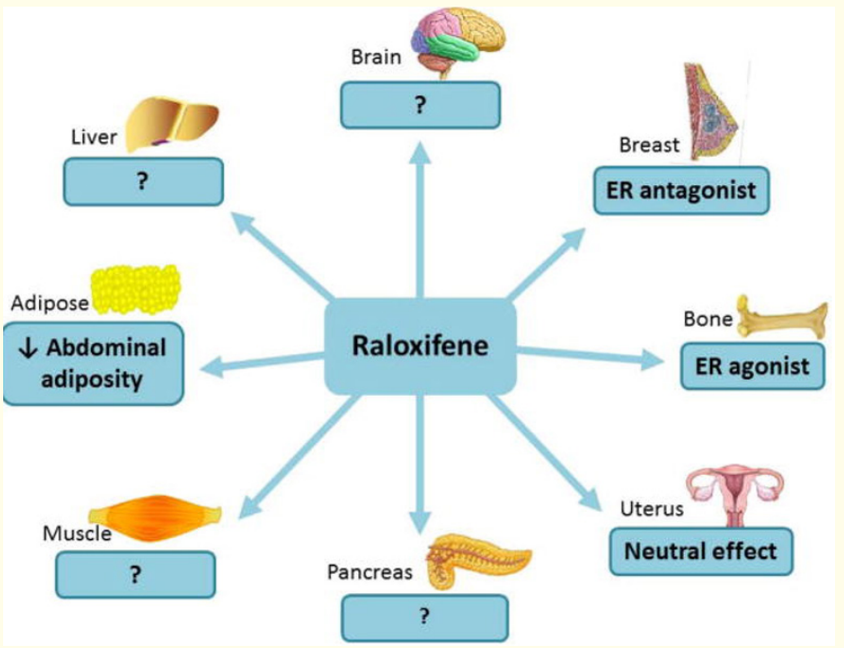

Figure 3: Summary of the effects of raloxifene

Courtesy ref no -31-Raloxifene is an ER agonist in bone and acts as ER antagonist in breast. It has a neutral effect in uterus. Raloxifene reduced fat mass in OVX female rodents and prevented abdominal adiposity in postmenopausal women. Raloxifene's effects on insulin sensitivity are controversial.

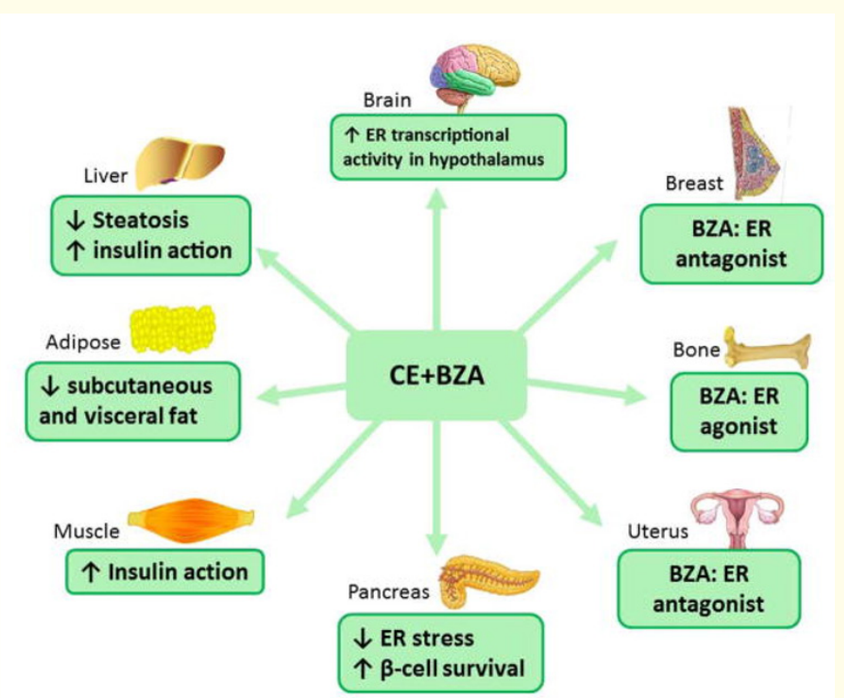

Figure 4: Summary of the effects of the combination bazedoxifene with CE.

Courtesy ref no -31-Bazedoxifene acts as an ER antagonist in breast and uterus while it is an ER agonist in bone. In rodent models of menopause, CE/BZA prevents obesity, reduces hepatic steatosis formation, and improves liver and muscle insulin sensitivity as well as glucose homeostasis.

Conclusion

Thus Postmenopausal symptoms are systemic symptoms correlated with estrogen deficiency subsequent to menopause. Currently treatments for postmenopausal symptoms are inclusive of include hormonal therapy (HT) as well as non-HT. Nevertheless the, ideal regimen pertaining to the balancing the advantages along with risks continue to be unclear. This article by Pan., *et al*. [32], reviewed the properties, regimens, in addition to inimical sequelae of drugs used in hormonal as well as non-HT. Nevertheless, HT is still continues to be the maximum efficacious treatment with safety in early beginning since menopause initiation. However, it is necessary to asssess the risks of associated chronic diseases and tailor personalized individualized treatments. Plausible estetrol preparations as well as greater kinds of tissue selective estrogen complex formulations are probable trajectories of drug generation in the future of HT. with regards to non-HT, fezolinetant, in phase III clinical trials, is poised to become a first-in-class therapy for vasomotor symptoms. Ospemifene, dehydroepiandrosterone (DHEA), in addition to vaginal lasers can further be used for moderate-to-severe genitourinary syndrome of menopause. Recent data suggest a superior efficacy and safety of vaginal lasers, however, greater corroborated proof Rregarding proof of long-term tolerability is required to react to the United States Food and Drug Administration warning. Herbal medication commonly used in Asia is efficacious in alleviating menopausal symptoms; nevertheless, its inimical sequelae still need greater detailed reports along with standardized observation methods. Pan*., et al*. [31], reviewed to provide a greater insight of drugs for the treatment of postmenopausal symptoms in addition to yield s useful information for clinical drug selection.

There fore here we yield useful information regarding the alteration in the working of the SERMs in HRT. It highlights the significance of the gaining understanding of the close crosstalk estrogen as well as its receptors in variable tissues. This yields greater insight into the complicated modes via which SERM work in the form of agonists in addition to antagonists. It further describes the clinical utilization of SERMs for instance avoidance of osteoporosis, treatment of the breast cancer in addition to relieving postmenopausal symptoms. It further describes the plausible benefits of SERMs inclusive of VVA treatment, relief of vasomotor symptoms, avoidance of osteoporosis along with CVD in women going via menopause. Furthermore, we further detail the continued generation of innovative SERMs for instance lasofoxifene, bazedoxifene, arzoxifene, along with ospemifene which yields safety in addition to are maximum efficacious. Thus this is a source for treating practitioners how there are changing needs of these postmenopausal women. Further extrapolations of these newer SERMs is treatment of endometriosis [33], Hepatocellular carcinoma (HCC) [34], avoid MetS as well asT2D. Earlier we had reviewed the role of bisphonates in prevention of osteoporosis, here we have updated part of newer SERMs as bisphonates cant be continued for long in view of fear of osteonecrosis of jaw etc [35].

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