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(54) Title: COMPOSITIONS AND METHODS FOR ALLEVIATING MENOPAUSAL SYMPTOMS

(57) Abstract

A method of alleviating climacterial menopausal and post-menopausal symptoms in females comprises administering an effective amount of a composition comprising melatonin and at least one estrogen and/or at least one androgen.

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COMPOSITIONS AND METHODS FOR ALLEVIATING MENOPAUSAL SYMPTOMS

Field of the Invention

This invention relates to a method of alleviating menopausal symptoms in women. More specifically, the invention relates to a method of alleviating climacterial menopausal and post-menopausal symptoms which comprises administering an effective amount of a composition comprising melatonin and at least one estrogen and/or at least one androgen.

Background of the Invention

The basic physiological and hormonal change associated with menopause in human females is a cessation of the cyclic follicular growth and maturation. A woman who is in menopause will not ovulate and will not have the associated menstrual bleeding which normally accompanies the ovulatory cycle. Menopause can begin physiologically as part of a woman's life cycle, signifying the end of her reproductive life cycle. A woman also can begin menopause as a result of the surgical removal of her ovaries or as a part of a pathological form of ovarian failure.

In menopause a woman's ovarian estradiol synthesis and secretion comes to a gradual end. As a result,

about sixty percent of her natural estrogen production is stopped; the peripheral tissue aromatization of androstenedione, which originates in the ovaries and the adrenal cortex, continue to sustain the remaining forty percent in the form of estrone. The quantity of estrone which is produced during menopause, however, is inadequate to support the estrogen requirements of estrogen dependent target organs, such as the hypothalamus, pituitary, breasts, urogenital tract and bone metabolism, in many women.

The relative insufficiency of estrogen produces an atrophy of epithelia and a significant decrease in the blood supply to estrogen target organs. As a direct result of this phenomenon, women in menopause experience symptoms of instability of their hypothalamic thermoregulatory centers, and many suffer from recurrent symptoms known as "hot flashes." Women suffering from "hot flashes" can experience nervousness, insomnia, fatigue, and/or depression. Peripheral estrogenic target organs also are affected by the decline in plasma estradiol, and symptoms of vaginal irritation, dyspareunia, dysuria vaginal infections and pruritus are common.

The mineralization of bone matrix is also affected significantly by the estrogen deficiency, resulting in a pathological condition known as osteoporosis. This condition is associated with significant morbidity and mortality, primarily as a result of hip fractures, although other bone fractures also are common.

The medical community is in general agreement that, if estrogen could be administered without risk, all women in the menopausal phase of their life cycle should receive estrogen medication to counteract and abolish the significant health risks which result from

estrogen deficiency. To date, however, there have been substantial risks associated with the administration of estrogen, such that only periodic and cautious medication with estrogen is advised.

Current regimens of estrogen medication typically utilize ethinyl estradiol or its methyl ether and/or conjugated estrogens. Dosages are kept as low as is practically possible to achieve some benefit with a minimum of risk. Typical dosages range from about 0.2 mg to about 1 mg daily.

As noted above, the administration of estrogen has been accompanied by many risks which have prevented their more common and widespread use. Potential risks include a higher risk of endometrial cancer, breast cancer and benign breast and liver tumors. Gallbladder disease also is more common among women who take estrogen, as are such systemic problems as hypertension and water retention.

To decrease the risk of developing any of these problems, it generally is recommended to administer estrogens in a cyclic fashion and to combine their administration with a progestin, which is thought to reduce the risks which are associated with long-term estrogen use.

In addition, it has been found that estrogen supplements do not lessen menopausal symptoms in some women unless given at very high doses. In some cases, such women have been given doses of an androgen, such as methyltestosterone, in place of estrogen supplementation, as a means of alleviating their symptoms. This type of therapy, however, also has been accompanied by the risk of developing significant negative side effects, including endometriosis and hyperplasia.

In view of the drawbacks and negative side effects of conventional estrogen supplementation and estrogen and androgen medication, new methods of alleviating menopausal and post-menopausal symptoms are sought. Accordingly, it is an object of this invention to provide a method for alleviating menopausal symptoms which is highly effective and provides the benefits and avoids the adverse effects associated with conventional estrogen therapy.

Summary of the Invention

In accordance with the present invention, there is disclosed a method for alleviating or preventing menopausal and post-menopausal symptoms in women suffering from or susceptible to such symptoms which comprises administering effective dosages of melatonin in combination with one or more estrogens, and/or one or more androgens. As used herein, "menopausal and post-menopausal symptoms include, for example, atrophic vaginitis, kraurosis vulvae, hypogonadism, osteoporosis and vasomotor symptoms.

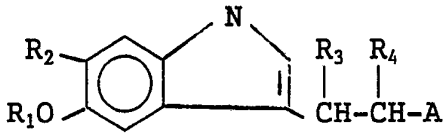
Detailed Description of the Invention

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesized and secreted by the pineal gland. The exact role of the hormone has not yet been determined. Studies have shown that in rodent species the hormone has an inhibitory effect on the gonads and their development. The daily injection of melatonin into Syrian golden hamsters has had an inhibitory effect on the development of the gonads, the weight of the testes of males and on ovulation in females.

Female rats injected with melatonin at certain times of the day also showed an inhibition of ovulation. Published results of studies wherein other mammalian species were injected with melatonin have not revealed similar results. Exogenous melatonin administration in humans has been studied in conjunction with a hypothesis that an abnormal melatonin rhythm is associated with endogenous depression and for pharmokinetic purposes (Waldhauser, Neuroendocrinology 39:307, 313 [1984]) and in connection with sleep-wake rhythms and the phenomenon of "jet-lag" following airplane trips associated with change in time zones.

The pineal gland undergoes a process of calcification which is directly related to age. Concomitant with this calcification, a significant decrease in serum melatonin has been reported. The present invention is based on the discovery that the administration of pharmacological doses of melatonin in combination with estrogen supplementation to menopausal women results in an alleviation of menopausal symptoms while minimizing the risks that have accompanied conventional estrogen therapy. The administration of melatonin increases the tolerance level for potent doses of estrogen.

As used herein, the term melatonin also encompasses melatonin analogs which, when administered in combination with an estrogen to a woman in menopause, increases the woman's tolerance for the estrogen. Such melatonin analogs can have the general formula:



wherein R_1, R_3 and R_4, individually, are hydrogen or an alkyl group having 1 to about 4 carbon atoms, R_2 is selected from hydrogen, hydroxy or an alkoxy group having from 1 to about 4 carbon atoms, and A is either -OH or -NH-C-R_5, wherein R_5 is either hydrogen or an alkyl group having from 1 to about 4 carbon atoms, provided that if A is NH-C-R_5, and R_1 and R_5 are both methyl and R_2 is hydrogen, both of R_3 and R_4 are not hydrogen. Preferred compounds are those in which R_2 is hydrogen or methoxy, with hydrogen being most preferred. Melatonin analogs encompassed within this definition include N-acetyl serotonin, N-acetyl, 5-hydroxy, 6-methoxytryptamine, 6-hydroxy-melatonin, 5-hydroxytryptophol and 5-methoxytryptophol, with N-acetyl serotonin being preferred.

The melatonin (or melatonin analog) desirably is administered in dosages sufficient to restore the patient's level of melatonin to her pre-menopausal limits or above.

As used herein the word estrogen refers both to conjugated estrogens, obtained directly from natural sources, and to synthetic estrogens. Conjugated estrogens include estrone, equilin, 17-α-dihydroequilin, 17-α-estradiol, equilenin and 17-α-dihydroequilenin. Typically, these products are administered as the salts of their sulfate esters. Preferred synthetic estrogens include ethinyl estradiol (i.e. 17α-ethynyl-3,17β-dihydroxy-estra-1,3,5(10)-triene) and mestranol (17α-ethynyl-17β-hydroxy-3-methoxy-estra-1,3,5(10) triene). Other useful synthetic estrogens include estradiol (3,17β-dihydroxy-

estra-1,3,5(10)-triene), estriol (3,16,17β-trihydroxy-estra-1,3,5(10)-triene), estrone (3-hydroxy-estra-1,3,5(10)triene-17-one), diethylstilbestrol, quinestradiol (3-cyclopentyloxy-16α, 17β-dihydroxy-estra-1,3,5(10)-triene) and estrone sulfate.

One embodiment of this invention is directed to compositions comprising melatonin and at least one estrogen. Depending upon the particular symptoms to be alleviated or prevented, the melatonin and estrogen can be administered to women orally, parenterally, in the form of an implant or as a vaginal cream or lotion. Administration is most convenient when the hormones are in oral dosage form, such as capsules, tablets, suspensions or solutions. Capsules or tablets are preferred. Capsules can be prepared by mixing the compound with a pharmaceutically-acceptable excipient and then filling gelatin capsule with the mixture in accordance with conventional procedures. Alternatively, the hormones can be mixed with one or more lubricants, such as stearic acid or magnesium stearate, flavor ameliorating agents, disintegrating elements, including potato starch, calcium phosphate tribasic and alginic acid, binders, such as gelatin, carnauba wax and corn starch, and/or tablet bases including lactose, corn starch, talc and sucrose, and then pressed into tablets.

As an alternative to oral administration, the melatonin and estrogen can be administered parenterally or in the form of a solid implant. For parenteral administration, the melatonin and estrogen are provided in injectable doses of a solution or suspension of the hormones in a physiologically acceptable diluent with a pharmaceutical carrier. The carrier can comprise water or an oil and optionally also can contain a surfactant

or other pharmaceutically acceptable adjuvant. Suitable oils include those of animal, vegetable, petroleum or synthetic origin, including peanut, soybean, corn, sesame, castor and mineral oil. Preferred liquid carriers include water, saline, aqueous sugar solutions, and glycols such as propylene glycol or polyethylene glycol.

The melatonin and estrogen also can be administered in the form of an implant, which is formulated such that it will provide a sustained release of the hormones over time. To make the implant, the hormones can be compressed into small cylinders and placed inside a physiologically acceptable shell material, such as a biodegradable or porous polymer, in accordance with conventional implant technology.

Alternatively, the estrogen and melatonin can be provided in the form of a cream or lotion. The cream or lotion is prepared using conventional bases, such as glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin and/or mineral oil in accordance with procedures well-known in the art.

A number of regimens are suitable for administering a combination of melatonin and estrogen. The particular regimen selected is dependent upon such factors as the number and severity of the particular symptoms or conditions to be treated and the method of administration. Lower doses of the hormone typically are needed for administration by way of an injection or implant than for oral administration. Generally, the estrogen is administered in the range of about 0.125 to about 15 mg per day. The melatonin is administered in an amount sufficient to increase the recipient's

physiological tolerance for estrogens and to reduce the negative side effects of conventional estrogen therapy to a minimal level. Generally, the melatonin is administered in the range of about 1 to about 2000 mg per day. The actual amount of estrogen and melatonin provided in each daily dose will depend upon the particular estrogen chosen, its relative potency, and the method of administration selected. For example, a lesser quantity of a more potent estrogen may achieve the same results as a larger quantity of a less potent estrogen. Synthetic estrogens generally are more potent than are natural estrogens. Thus, when a natural estrogen is used, the ratio of estrogen to melatonin generally will be higher than when a synthetic estrogen is used. In addition, lower dosages generally are needed for administration of an implant or intravenous or intramuscular injection than for oral administration. The hormones can be administered on a continuous basis or cyclically (i.e., one or both hormones is administered for a certain number of days and then withheld for a certain number of days), as illustrated in the particular suggested regimens set forth below.

In one example of a useful regimen, the melatonin and estrogen can be administered daily in oral form to women suffering from such conditions as atrophic vaginitis, kraurosis vulvae, or hypogonadism, for about 21 days, then for about the next 7 days either the melatonin is administered in the absence of the estrogen or both hormones are withheld. With either of these regimens, the cycle can be repeated as necessary. With these regimens, typically the estrogen is administered in a dose of about 1 to about 8 mg per day and the melatonin is administered in a dose of about 3

to about 2000 mg per day, preferably about 30 to about 300 mg per day.

In an alternative regimen, the estrogen and melatonin are orally administered for about 60-90 days, then both hormones are withheld until the symptoms reappear. With this regimen, given the length of time of continuous estrogen administration, the estrogen typically is administered in lower dosages than in the regimens discussed above. Generally the estrogen is administered in the range of about 0.3 to about 1.25 mg per day and the melatonin is administered in the range of about 30 to about 300 mg per day.

To alleviate osteoporosis or vasomotor symptoms, a combination of melatonin and estrogen can be administered orally on a daily, chronic basis in amounts generally ranging from about 0.125 to about 2.5 mg estrogen per day and about 3 to about 2000 mg, preferably about 30 to about 300 mg, melatonin per day. Alternatively, the estrogen can be administered in the same general amounts for about 21 days in combination with the melatonin, then the estrogen is withheld for about the next 7 days. During this seven day period, the melatonin also can be withheld or its administration can be continued.

If the melatonin and estrogen are to be administered by intravenous or intramuscular injection, the hormones conveniently can be provided in the form of lyophilized cakes prior to being placed into solution and injected. For example, to prepare lyophilized cakes, about 5 to about 150 mg estrogen, preferably about 20 to about 30 mg estrogen, and about 1 to about 10 grams melatonin, preferably about 3 to about 7 grams melatonin, can be mixed with a conventional base or excipient, such as lactose or

sodium citrate, and lyophilized. The cake then can be dissolved in a sterile diluent, such as sterile water or benzyl alcohol, to achieve the desired final hormone concentrations, and the pH of the solution can be adjusted, if necessary, to assure that the solution is physiologically acceptable with sodium hydroxide or hydrochloric acid. Individual daily doses then can be obtained from this master stock solution.

If the estrogen and melatonin are prepared in the form of a cream or lotion, as discussed above, each gram of the cream or lotion desirably contains about 0.2 to 2.5 mg estrogen and about 0.1 to 3 mg melatonin, preferably about 0.6 mg estrogen and about 0.5 mg to about 3 mg melatonin. Administration of the hormones in this fashion is especially beneficial for the alleviation of symptoms of kraurosis and atrophic vaginitis. The cream or lotion is applied locally one to about ten times a day for as many days as needed. Ideally, the medication is applied about four times a day for about 21 days, then is withheld for about 7 days, the cycle being repeated as necessary.

In any of the foregoing embodiments, if desired, the melatonin and estrogen can be administered in combination with a progestogen. Progestogens have been administered with conventional estrogen therapy to lessen the risk of endometrial hyperplasia associated with the administration of estrogen and can be included in the compositions of this invention to achieve the same benefits. Any progestationally active compound is suitable for use as the progestogen component in the present invention. Suitable progestogens include progesterone and derivatives thereof. The presently preferred progestogen is norethindrone (i.e., 19-nor-17α-ethynyl-17β-hydroxy-4-androsten-3-one) and

norgestrel (13β-ethyl-17α-ethynyl-17βhydroxygon-4-en-3-one). Other progestogens include chlormadinone-acetate (6-chloro-17-hydroxy-pregna-4,6-diene-3,20-dione acetate), norethynodrel (17α-ethynyl-17-hydroxy-estr-5(10)-en), medroxyprogesterone acetate (17α-acetoxy-6α-methyl-pregn-4-ene-3,20-dione), megestrol acetate (17α-acetoxy-6-methyl-pregna-4,6-diene-3,20-dione), lynestrenol (17α-ethynyl-17β-hydroxy-estr-4-en-3-one), quingestrone (3-cyclopentyloxy-pregna-3,5-diene-20-one), norethindrone acetate (17β-acetoxy-17α-ethynyl-estr-4-en-3-one), ethynodiol acetate (3β,17β-diacetoxy-17α-ethynyl-estr-4-one), dimethisterone [17β-hydroxy-6α-methyl-17-(1-propynyl)-androst-4-en-3-one], and levonorgestrel.

In the regimens described above, the progestogen can be administered with the estrogen and melatonin or it can be administered for a desired period of time immediately following withdrawal of the estrogen. For example, if estrogen and melatonin are administered orally for about 60-90 days, the progestogen can be administered in combination with the other hormones over the same period or it can be administered for about 7-14 days following the estrogen-melatonin therapy. The amount of progestogen administered depends upon the strength of the particular progestogen chosen, the method of administration and the length of time of administration. Typically, the progestogen is administered in daily doses of about 7.5 to about 2500 ug, preferably about 7.5 to about 600 ug.

In an alternative embodiment of this invention, the melatonin is combined with an androgen in place of, or in combination with, an estrogen. Preferred androgens include methyltestosterone and fluoxymesterone. It has been found that some of the

symptoms of menopause, such as vasomotor symptoms of estrogen deficiency, can be treated more effectively by including an androgen in the therapeutic regimen than by treating with estrogen alone or with a combination of estrogen and melatonin. Generally, the androgen is administered in a dose of about 0.2 to about 15 mg, preferably about 0.5 to about 2.5 mg, and the melatonin and estrogen are administered in the general ranges set forth above. This combination of hormones can be administered in acyclic fashion, as described above, or continuously, as needed.

In any of the suggested regimens set forth above, on those days that both the melatonin and one or more additional hormones are administered, they conveniently are combined and administered together, although they also can be administered separately.

In a preferred embodiment of this invention, the hormone compositions are administered in oral dosage form, preferably in the form of pills or capsules. The pills or capsules can be packaged in any manner suitable for proper delivery and use. If the pills are to be administered in accordance with a cyclic regimen, they preferably are packaged in the form of a kit or package in which the daily unit dosage forms are provided or arranged in a contiguous, sequential order which will enable the woman taking the pills to take the proper formulation on any given day. Suitable kits or packages include the conventional bubble plastic package used for oral contraceptives containing individual bubbles for either 21 or 28 pills, depending upon the regimen selected, in a sheet of flexible plastic. The bubbles are sealed by a sheet of plastic which can break and release a pill when the bubble is pressed. On the first day of medication, the first

pill in the sequence is removed from the individual slot and taken. The next pill in the sequence is taken the next day and so on thereafter until the dispenser is empty. A new dispenser is begun 28 days after the first dispenser was begun. If a 21 day regimen is to be followed, an additional 7 pills, each containing only a placebo, can be included in the dispenser package, if desired, so that a pill is taken every day of the cycle.

In addition to alleviating various menopausal and post-menopausal symptoms, the compositions of this invention also can be administered on a preventive basis, especially to prevent osteoporosis. A woman found to be at risk can be given a composition in accordance with this invention, containing relatively low doses of the hormones, on a continuous, daily basis.

Claims

1. A method of alleviating or preventing menopausal or post-menopausal symptoms in a woman suffering from or susceptible to such symptoms which comprises administering orally, intravenously or in the form of an implant on a daily basis an effective amount of melatonin in combination with one or more estrogens, one or more androgens or both an androgen and an estrogen.

2. The method of claim 1 wherein the melatonin is administered in combination with one or more estrogens and the daily dosage of melatonin is sufficient to increase the female's physiological tolerance for the estrogen administered.

3. The method of claim 2 wherein the daily dosage level of estrogen ranges from about 0.125 mg to about 15 mg and the daily dosage level of the melatonin ranges from about 1 mg to about 2000 mg.

4. The method of claim 2 wherein the estrogen is selected from the group consisting of estrone, equilin, 17-α-dihydroequilin, 17-α-estradiol, equilenin and 17-α-dihydroequilenin.

5. The method of claim 4 wherein the estrogen is administered in the form of its sulfate ester salt.

6. The method of claim 2 wherein an estrogen is selected from the group consisting of ethinyl estradiol, mestranol, estradiol, estriol, estrone, diethylstilbestrol, quinestradiol and estrone sulfate.

7. The method of claim 1 wherein a melatonin analog, which when combined with an estrogen and/or an androgen is effective in alleviating or preventing menopausal symptoms, is administered in place of melatonin.

8. The method of claim 3 wherein the daily dosage level of the estrogen is from about 1 mg to about 8 mg, the daily dosage of melatonin is from about 3 mg to about 2000 mg and the estrogen and melatonin are administered orally.

9. The method of claim 8 wherein the daily dosage level of melatonin is from about 30 mg to about 300 mg.

10. The method of claim 8 which comprises administering daily for about 21 days a combination of estrogen and melatonin followed by administering melatonin daily for about 7 days in the absence of an estrogen.

11. The method of claim 8 which comprises administering daily for about 21 days a combination of estrogen and melatonin followed by about 7 days without melatonin or estrogen administration.

12. The method of claim 8 wherein the estrogen and melatonin are administered for about 60 to about 90 days, then both the estrogen and melatonin are withheld until the menopausal or post-menopausal symptoms reappear.

13. The method of claim 12 wherein the daily dosage of estrogen is from about 0.3 mg. to about 1.25 mg and the daily dosage of melatonin is about 30 mg. to about 300 mg.

14. The method of claim 3 wherein the daily dosage of estrogen is from about 0.125 mg to about 2.5 mg, the daily dosage of melatonin is from about 3 mg to about 2000 mg and the estrogen and melatonin are administered orally.

15. The method of claim 14 wherein the daily dosage of melatonin is from about 30 mg to about 300 mg.

16. The method of claim 14 or 15 which comprises administering daily for about 21 days a combination of estrogen and melatonin, followed by administering melatonin daily for about 7 days in the absence of estrogen.

17. The method of claim 14 or 15 which comprises administering daily for about 21 days a combination of estrogen and melatonin, followed by about 7 days without estrogen or melatonin administration.

18. The method of claim 3 wherein the method of administration is by intravenous injection in a physiologically suitable carrier.

19. The method of claim 3 wherein the method of administration is by implant.

20. The method of claim 2 wherein a progestogen is administered in combination with the melatonin and one or more estrogens.

21. The method of claim 20 wherein the progestogen is selected from the group consisting of norethindrone, norgestrel, chlormadionone-acetate, norethynodrel, medoxyprogesterone acetate, megesterol acetate, lynestrenol, quingestrone, norethindrone acetate, ethynodiol acetate, dimethisterone, and levonorgestrel.

22. The method of claim 1 wherein the melatonin is administered in combination with at least one androgen.

23. The method of claim 1 wherein the melatonin is administered in combination with at least one estrogen and at least one androgen.

24. The method of claim 22 or 23 wherein the androgen is methyltestosterone or fluoxymesterone.

25. The method of claim 22 wherein the daily dosage of androgen is from about 0.2 mg to about 15 mg

and the daily dosage of melatonin is from about 1 mg to about 2000 mg.

26. The method of claim 23 wherein the daily dosage of the androgen is from about 0.2 mg to about 15 mg, the daily dosage of estrogen is from about 0.125 mg to about 15 mg and the daily dosage of melatonin is from about 1 mg to about 2000 mg.

27. A method for effecting estrogen supplementation in a menopausal or post-menopausal woman which comprises administering orally, intravenously or in the form of an implant effective doses of one or more estrogens in combination with a sufficient amount of melatonin to increase the woman's physiological tolerance for estrogen.

28. A method for treating osteoporosis which comprises administering orally, intravenously or in the form of an implant to a woman in need of such treatment an effective amount of a composition comprising melatonin in combination with at least one estrogen and/or at least one androgen.

29. A method for preventing osteoporosis in a woman susceptible to developing osteoporosis which comprises administering orally, intravenously or in the form of an implant effective amounts of melatonin in combination with at least one estrogen and/or at least one androgen.

30. A method for treating atrophic vaginitis which comprises administering orally, intravenously or in the form of an implant to a woman in need of such treatment an effective amount of a composition comprising melatonin in combination with at least one estrogen and/or at least one androgen.

31. A method of treating kraurosis vulvae which comprises administering orally, intravenously or in the

form of an implant to a woman in need of such treatment an effective amount of a composition comprising melatonin in combination with at least one estrogen and/or at least one androgen.

32. A method of treating vasomotor symptoms of estrogen deficiency which comprises administering orally, intravenously or in the form of an implant to a woman in need of such treatment an effective amount of a composition comprising melatonin in combination with at least one estrogen.

33. A composition suitable for alleviating or preventing menopausal or post-menopausal symptoms in a human female which comprises a combination of melatonin and one or more estrogens and/or one or more androgens effective to alleviate or prevent said symptoms; wherein said composition is in a form suitable for administration orally, intravenously or in the form of an implant.

34. A composition in accordance with claim 33 which comprises melatonin in combination with at least one estrogen and the amount of melatonin in the composition is sufficient to increase the female's physiological tolerance for the estrogen in the composition.

35. The composition of claim 34 which comprises daily dosage levels of estrogen which range from about 0.125 mg to about 15 mg and daily dosage levels of melatonin which range from about 1 mg to about 2000 mg.

36. The composition of claim 34 wherein the estrogen is selected from the group consisting of estrone, equilin, 17-α-dihydroequilin, 17-α-estradiol, equilenin and 17-α-dihydroequilenin.

37. The composition of claim 36 wherein the estrogen is administered in the form of its sulfate ester salt.

38. The composition of claim 34 wherein the estrogen is selected from the group consisting of ethinyl estradiol, mestranol, estradiol, estriol, estrone, diethylstilbestrol, quinestradiol and estrone sulfate.

39. The composition of claim 33 wherein a melatonin analog effective in alleviating menopausal symptoms is substituted for melatonin.

40. The composition of claim 34 which is in oral dosage form and the daily dosage level of the estrogen is from about 1 mg to about 8 mg and the daily dosage level of melatonin is from about 3 mg to about 2000 mg.

41. The composition of claim 40 wherein the daily dosage level of melatonin is from about 30 mg to about 300 mg.

42. The composition of claim 40 which comprises about 21 daily doses of a combination of estrogen and melatonin and about 7 daily doses of melatonin.

43. The composition of claim 40 which comprises about 21 daily doses of a combination of estrogen and melatonin.

44. The composition of claim 40 which comprises about 60 to about 90 daily doses of a combination of the estrogen and melatonin.

45. The composition of claim 35 which is in oral dosage form and the daily dosage of estrogen is from about 0.125 mg to about 2.5 mg and the daily dosage of melatonin is from about 3 mg to about 2000 mg.

46. The composition of claim 45 wherein the daily dosage of melatonin is from about 30 mg to about 300 mg.

47. The composition of claim 45 which comprises about 21 daily doses of a combination of estrogen and melatonin, and about 7 daily doses of melatonin.

48. The composition of claim 45 which comprises about 21 daily doses of a combination of estrogen and melatonin.

49. The composition of claim 34 which is suitable for administration by intravenous injection in a physiologically suitable carrier.

50. The composition of claim 34 which is suitable for administration by implant.

51. The composition of claim 33 which comprises an effective amount of a combination of melatonin and at least one androgen.

52. The composition of claim 33 which comprises an effective amount of a combination of melatonin, an estrogen and an androgen.

53. The composition of claim 51 or 52 wherein the androgen is methyltestosterone or fluoxymesterone.

54. The composition of claim 51 which comprises daily dosage levels of androgen of about 0.2 mg to about 15 mg and daily dosage levels of about 1 to about 2000 mg.

55. The composition of claim 52 which comprises daily dosage levels of the androgen which range from about 0.2 mg to about 15 mg, daily dosage levels of estrogen which range from about 0.125 mg to about 15 mg and daily dosage levels of melatonin which range from about 3 mg to about 2000 mg.

56. The composition of claim 55 wherein the daily dosage of androgen is from about 0.5 mg to about 2.5 mg and the daily dosage of melatonin is from about 30 mg to about 300 mg.

57. A composition for effecting estrogen supplementation in a menopausal or post-menopausal woman which comprises estrogen supplementation-effective doses of an estrogen in combination with a sufficient amount of melatonin to increase the woman's physiological tolerance for the estrogen; wherein said composition is in a form suitable for administration orally, parenterally or as an implant.

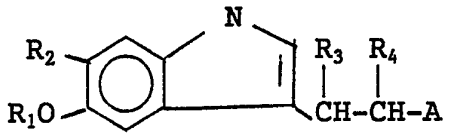
58. A composition for treating or preventing osteoporosis which comprises a combination of melatonin and at least one estrogen and/or at least one androgen effective to prevent or treat osteoporosis; wherein said composition is in a form suitable for administration orally, parenterally or as an implant.

59. A composition for treating atrophic vaginitis which comprises a combination of melatonin and at least one estrogen and/or at least one androgen effective to treat atrophic vaginitis; wherein said composition is in a form suitable for administration orally, parenterally or as an implant.

60. A composition for treating kraurosis vulvae which comprises a combination of melatonin and at least one estrogen and/or at least one androgen effective to treat kraurosis vulvae; wherein said composition is in a form suitable for administration orally, parenterally or as an implant.

61. A composition for treating vasomotor symptoms of estrogen deficiency which comprises a combination of melatonin and at least one estrogen and/or at least one androgen effective to treat said symptoms; wherein said composition is in a form suitable for administration orally, parenterally or as an implant.

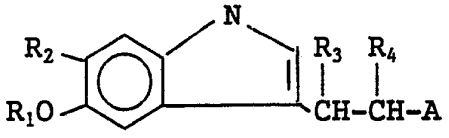
62. The method of claim 7 wherein the melatonin analog has the general formula



wherein R_1, R_3 and R_4, individually, are hydrogen or an alkyl group having 1 to about 4 carbon atoms, R_2 is selected from hydrogen, hydroxy or an alkoxy group having from 1 to about 4 carbon atoms, and A is either -OH or $-NH-\overset{\overset{O}{\|}}{C}-R_5$, wherein R_5 is either hydrogen or an alkyl group having from 1 to about 4 carbon atoms, provided that if A is $NH-\overset{\overset{O}{\|}}{C}-R_5$, and R_1 and R_5 are both methyl and R_2 is hydrogen, both of R_3 and R_4 are not hydrogen. Preferred compounds are those in which R_2 is hydrogen or methoxy, with hydrogen being most preferred. Melatonin analogs encompassed within this definition include N-acetyl serotonin, N-acetyl, 5-hydroxy, 6-methoxytryptamine, 6-hydroxy-melatonin, 5-hydroxytryptophol and 5-methoxytryptophol, with N-acetyl serotonin being preferred.

63. The method of claim 62 wherein the melatonin analog is N-acetyl serotonin, N-acetyl, 5-hydroxy, 6-methoxy tryptamine, 6-hydroxy-melatonin, 5-hydroxytryptophol, or 5-methoxytryptophol.

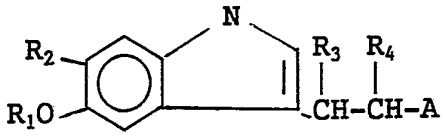
64. The composition of claim 39 wherein the melatonin analog has the general formula



wherein R_1, R_3 and R_4, individually, are hydrogen or an alkyl group having 1 to about 4 carbon atoms, R_2 is selected from hydrogen, hydroxy or an alkoxy group

having from 1 to about 4 carbon atoms, and A is either -OH or -NH-C-R_5, wherein R_5 is either hydrogen or an alkyl group having from 1 to about 4 carbon atoms, provided that if A is NH-C-R_5, and R_1 and R_5 are both methyl and R_2 is hydrogen, both of R_3 and R_4 are not hydrogen. Preferred compounds are those in which R_2 is hydrogen or methoxy, with hydrogen being most preferred. Melatonin analogs encompassed within this definition include N-acetyl serotonin, N-acetyl, 5-hydroxy, 6-methoxytryptamine, 6-hydroxy-melatonin, 5-hydroxytryptophol and 5-methoxytryptophol, with N-acetyl serotonin being preferred.

65. The composition of claim 64, wherein the melatonin analog is:



wherein R_1, R_3 and R_4, individually, are hydrogen or an alkyl group having 1 to about 4 carbon atoms, R_2 is selected from hydrogen, hydroxy or an alkoxy group having from 1 to about 4 carbon atoms, and A is either -OH or -NH-C-R_5, wherein R_5 is either hydrogen or an alkyl group having from 1 to about 4 carbon atoms, provided that if A is NH-C-R_5, and R_1 and R_5 are both methyl and R_2 is hydrogen, both of R_3 and R_4 are not hydrogen. Preferred compounds are those in which R_2 is hydrogen or methoxy, with hydrogen being most preferred. Melatonin analogs encompassed within this definition include N-acetyl serotonin, N-acetyl, 5-

hydroxy, 6-methoxytryptamine, 6-hydroxy-melatonin, 5-
25 hydroxytryptophol and 5-methoxytryptophol, with N-
acetyl serotonin being preferred.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/00235

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/565 //(A 61 K 31/565 A 61 K 31:40)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO,A,8807370 (APPLIED MEDICAL RESEARCH, LTD) 6 October 1988, see page 12, lines 10-25	33-61, 64,65

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06-09-1991	15. 10. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 1-32,62,63 because they relate to subject matter not required to be searched by this Authority, namely:

Please see rule 39.1(iv) - PCT:
Methods for treatment of the human or animal body
by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a)

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple Inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9100235 SA 44086

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8807370	06-10-88	US-A- 4855305	08-08-89
		AU-A- 1683088	02-11-88
		EP-A- 0354921	21-02-90
		JP-T- 2502724	30-08-90
		ZA-A- 8802079	15-09-88