

## Venlafaxine의 안면홍조 증상개선효과에 대한 최근 연구 고찰

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### Venlafaxine for Management of Hot Flashes: A Review of Randomized Controlled Trials in Human

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안면홍조는 폐경기 초기 많은 여성들에게 나타나는 증상이다. 정확한 원인은 밝혀지지 않았지만 혈중 에스트로겐 수치가 낮아졌을 때 안면홍조 증상이 나타나기 때문에 에스트로겐을 기본으로 한 호르몬 요법이 수년간 안면홍조 증상 치료의 중심이었다. 그러나 호르몬 요법이 유방암, 뇌졸중 등의 발생 위험도를 증가시킨다는 연구 결과가 발표된 이후 많은 보건의료인들은 호르몬 요법 대신 사용할 수 있는 다른 치료제에 관심을 보이고 있다. 본 연구는 venlafaxine의 안면홍조 증상 치료효과에 대한 최신 지견을 얻고자, 1990년부터 2010년 7월까지 MEDLINE에 등재된 논문을 Hot flashes와 Venlafaxine이라는 MeSH terms로 검색하여 추출한 자료 중에서 대조군이 사용된 무작위 배정 및 이중맹검 임상연구 사례만을 선별하여 임상적 유용성을 평가하였다. 현재 venlafaxine은 안면홍조 증상 치료제로 허가된 의약품은 아니지만 최근 여러 국가에서 시행된 연구들은 venlafaxine이 효과적인 안면홍조 증상 치료제일 수 있다는 결과를 보여주고 있다.

□ Key words - Venlafaxine; Hot flashes; Menopause

Hot flashes are the classic sign of menopause and the most troublesome symptom of women during the perimenopausal and early menopausal years. Hot flashes usually begin as a sudden sensation of heat centered on the face and neck area that rapidly becomes generalized. Since women experience hot flashes when their estrogen levels in blood are low or when estrogens are withdrawn after bilateral oophorectomy, estrogens are thought to be a main factor in etiology of hot flashes. So estrogen-based therapy has been the mainstay for treating hot flashes with high efficacy for many years. However, many health care providers now want to use nonhormonal therapies for patients with hot flashes because of the results of the Women's Health Initiative

study in 2002. The study showed increased rates of breast cancer, coronary artery disease, stroke, and pulmonary embolism in women treated with estrogen-progestin versus placebo. The exact cause of hot flashes is still unknown, but histamine, prostaglandins, serotonin, acetaldehyde, and substance P are proposed mediators of hot flashes. The mediators' potential interaction with the hypothalamic thermoregulatory center appears to be related to the pathophysiology of hot flashes.<sup>1-6)</sup> Recently, many studies suggested that antidepressant therapy may be effective for treatment of hot flashes. Among the antidepressants studied for management of hot flashes, venlafaxine is the agent investigated the most. The aim of this study is to assess the effect of venlafaxine on hot flashes by performing a systematic analysis. A MEDLINE search (from January 1990 to July 2010) was conducted using a combination search term hot flashes and venlafaxine with limits of random-

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ized controlled trials and humans.

## VENLAFAXINE

Venlafaxine is indicated for the treatment of major depressive disorder. The chemical name for venlafaxine is 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol hydrochloride. The molecular formula is  $C_{17}H_{27}NO_2 \cdot HCl$  and the molecular weight is 313.87.<sup>7-8)</sup> Venlafaxine and its active metabolite O-desmethylvenlafaxine (ODV) have antidepressive effects by blocking the reuptake of both serotonin and norepinephrine with no substantial affinity for muscarinic, cholinergic, histaminic H1 or  $\alpha$ -adrenergic receptors. Venlafaxine is a potent serotonin reuptake inhibitor regardless of the dose, and it is also a potent inhibitor of norepinephrine reuptake at higher doses (generally > 150 mg/d). Venlafaxine is well absorbed, reaching maximum plasma concentrations at 2 hours after oral administration in immediate release formulation. Renal elimination of venlafaxine and its metabolites is the primary route of excretion. The elimination half-life of venlafaxine is approximately 3-7 hours and ODV is 9-13 hours.<sup>9-11)</sup>

## LITERATURE REVIEW

Loprinzi CL, Kugler JW, Sloan JA, et al. conducted a 4-week, double-blind, placebo-controlled randomized study to assess the efficacy of venlafaxine for the treatment of hot flashes in survivors of breast cancer.<sup>12)</sup> Women who had a history of breast cancer or who were fearful of getting breast cancer from estrogen use were included. They had to have troublesome hot flashes, occurring at least 14 times per week for enrollment. A total of 229 participants were randomized to receive one of four treatments: (i) venlafaxine 37.5 mg/day for 4 weeks (the 37.5 mg/day group), (ii) venlafaxine 37.5 mg/day for 1 week, followed by 75 mg/day for 3 weeks (the 75 mg/day group), (iii) venlafaxine 37.5 mg/day for 1 week, followed by 75 mg/day for 1 week, then 150 mg/day for 2 weeks (the 150 mg/day group), or (iv) placebo for 4 weeks (the placebo group). At week 4, the median hot flash scores signifi-

cantly decreased from baseline ( $p < 0.001$  for comparison of the treatment groups with the placebo group) by 27% (95% CI, 11-34) in the placebo group ( $n=50$ ), 37% (95% CI, 26-54) in the 37.5 mg/day group ( $n=49$ ), 61% (95% CI, 50-68) in the 75 mg/day group ( $n=43$ ), and 61% (95% CI, 48-75) in the 150 mg/day group ( $n=49$ ). Some adverse effects such as decreased appetite, nausea, mouth dryness, and constipation were occurred significantly more in the venlafaxine 75 mg/day and 150 mg/day groups ( $p < 0.05$  for comparison with the placebo group, except for constipation in the 75 mg/day group). There are limitations in this study. The treatment period of this study was short, and participants were primarily breast cancer survivors. Therefore, longer studies with general population should be conducted to use venlafaxine for the treatment of hot flashes in clinical practice.

A 12-week, randomized, double-blind, placebo-controlled study was conducted to test the efficacy of venlafaxine for the treatment of postmenopausal hot flashes.<sup>13)</sup> Researchers included 80 natural or surgical menopausal women who had more than 14 hot flashes per week. Participants were randomly assigned to receive either venlafaxine 37.5 mg/day for 1 week, followed by 75 mg/day for 11 weeks ( $n=40$ ) or placebo for 12 weeks ( $n=40$ ). Of the 61 patients who completed the study, 29 were in the venlafaxine group and 32 were in the placebo group. At week 12, hot flash scores decreased significantly from baseline ( $p < 0.001$ ) in the venlafaxine group (51%) compared with in the placebo group (15%). The venlafaxine group had significantly more dry mouth (81% vs. 44%), sleeplessness (88% vs. 47%), decreased appetite (81% vs. 53%) as adverse effects than the placebo group. Treatment period of this study was relatively longer compared to the study mentioned earlier. That the inclusion criteria was not breast cancer patients was also different than the first study reviewed in this paper.

Another 6-week, randomized, controlled study tested venlafaxine as treatment for hot flashes.<sup>14)</sup> To be eligible for this study, women had to have troublesome hot flashes, occurring at least 14 times per week for at least 1 month. A total of 218 patients were randomized to

receive either venlafaxine 37.5 mg/day for 1 week, followed by 75 mg/day for 5 weeks or medroxyprogesterone acetate (MPA) 400 mg intramuscularly for one dose. During the study period, hot flash scores decreased significantly in the venlafaxine group, but MPA was more effective than venlafaxine in reducing hot flash scores (at week 6, mean reductions from baseline: 79% in the MPA group, 55% in the venlafaxine group,  $p < 0.0001$ ). In the first treatment week, the venlafaxine group had significantly more nausea ( $p < 0.0001$ ), appetite loss ( $p < 0.0001$ ), dizziness ( $p = 0.007$ ), constipation ( $p = 0.001$ ), mouth dryness ( $p = 0.01$ ), and sleepiness ( $p = 0.02$ ) than the MPA group. Study duration was short, but sample size was large.

Carpenter JS, Storniolo AM, Johns S, et al. conducted a 12-week, double-blind, randomized, placebo-controlled, crossover study to evaluate the effect of two doses of venlafaxine on hot flashes.<sup>15)</sup> Women with a history of breast cancer were included, and they had to have daily hot flashes ( $\geq 1$  per day). This study consisted of the low-dose study and the high-dose study. In the low-dose study, 52 participants were randomized to one of two different sequence groups: venlafaxine/placebo or placebo/venlafaxine. They received venlafaxine 37.5 mg/day for 6 weeks, then placebo for 6 weeks or vice versa. In the high-dose study, 18 women were randomized in the same way as the low-dose study. They received venlafaxine 37.5 mg/day for 1 week, followed by 75 mg/day for 4 weeks, then 37.5 mg/day for 1 week. After 6 weeks of the treatment period, they got placebo for another 6 weeks or vice versa. Both low and high doses of venlafaxine significantly reduced hot flash frequency compared with placebo ( $p < 0.001$  and  $p = 0.013$ , respectively). Patients in the low-dose study reported significantly more severe constipation ( $p = 0.001$ ), headaches ( $p = 0.007$ ), and dry mouth ( $p < 0.001$ ) compared with placebo, and those in the high-dose study showed significantly more severe trouble sleeping ( $p = 0.034$ ) than placebo. Sample size was small and the duration of active treatment was also short in this study.

In a 8-week, double-blind, randomized, crossover study, Loibl S, Schwedler K, von Minckwitz G, et al.

assessed venlafaxine as treatment for hot flashes in patients with breast.<sup>16)</sup> Women with primary breast cancer who had troublesome hot flashes were included. A total of 80 patients were randomly assigned to receive either venlafaxine 37.5 mg twice a day ( $n = 40$ ) or clonidine 0.075 mg twice a day ( $n = 40$ ) for 4 weeks. After 4 weeks of treatment period, patients crossed over to the other treatment. However, this crossover part of this study could not be assessed because of incomplete evaluation forms. At week 4, there was a 57% reduction in the hot flash frequency with venlafaxine compared with 37% with clonidine ( $p = 0.025$ ). The hot flash score also decreased by 39% in the venlafaxine group. Regarding adverse effects, nausea was occurred significantly more in the venlafaxine group than in the clonidine group ( $p = 0.05$ ). This study also has small sample size and short duration.

In the Netherlands, a 18-week, double-blind, randomized, crossover study was conducted to study the efficacy and toxicity of venlafaxine for hot flashes in breast cancer patients as compared to clonidine.<sup>17)</sup> This study enrolled 60 patients with breast cancer at the ages of less than 60, and they had to have more than 14 hot flashes per week. They were randomized in a 1:1 ratio to the venlafaxine/clonidine group or the clonidine/venlafaxine group. In the venlafaxine/clonidine group, patients received venlafaxine 75 mg/day for 8 weeks, followed by 2 weeks wash-out and 8 weeks of clonidine 0.05 mg twice a day, while patients in the clonidine/venlafaxine group received clonidine 0.05 mg twice a day for 8 weeks, followed by 2 weeks wash-out and 8 weeks of venlafaxine 75 mg/day. Both venlafaxine and clonidine reduced the hot flash scores (49% and 55%, respectively), but the difference between the two drugs was not significant ( $p = 0.55$ ). Venlafaxine caused more adverse effects than clonidine, and sleep disturbance occurred significantly more compared to baseline ( $p = 0.02$ ) in patients with venlafaxine.

Irani J, Salomon L, Oba R, et al. conducted a 10-week, double-blind, randomized study to evaluate the efficacy of venlafaxine for hot flashes in men with prostate cancer.<sup>18)</sup> This study included men with pros-

**Table 1. Summary of clinical studies of venlafaxine for the treatment of hot flashes**

Author	Study Design	Number of Subjects	Study Duration	Inclusion Criteria	Exclusion Criteria	Venlafaxine Dose	Outcomes
Loprinzi CL, Kugler JW, Sloan JA, <i>et al.</i> <sup>12)</sup>	randomized, double-blind, placebo-controlled	229	4 weeks	women with a history of breast cancer or fear of getting breast cancer from estrogen use; troublesome hot flashes, occurring at least 14 times per week; flashes severe enough for the patient to desire therapeutic intervention, and present for at least a month before study entry; age older than 18 years; life expectancy at least 6 months; performance status of 0–1 on the Eastern Cooperative Oncology Group scale	use of venlafaxine in the past; any antidepressant treatment within the preceding 2 years; pregnancy; breastfeeding; use of other medications to treat hot flashes within the previous 2 weeks; uncontrolled hypertension (persistent diastolic blood pressure >95 mm Hg, systolic blood pressure >160 mm Hg, or both)	37.5, 75, or 150 mg/day	Improved median hot flash scores
Evans ML, Pritts E, Vittinghoff E, <i>et al.</i> <sup>13)</sup>	randomized, double-blind, placebo-controlled	80	12 weeks	natural or surgical menopause; more than 14 hot flashes per week	known adverse reactions to antidepressant medications; use of estrogens, progestins, androgens, antidepressants, or chemotherapy	37.5 mg/day for 1 week, followed by 75 mg/day for 11 weeks	Improved hot flash scores
Loprinzi CL, Levitt R, Barton D, <i>et al.</i> <sup>14)</sup>	randomized, controlled	218	6 weeks	women with troublesome hot flashes, occurring at least 14 times per week for at least 1 month	treatment with antineoplastic chemotherapy, androgens, and/or estrogens; prior progestational therapy within the last year unless it was part of hormone replacement therapy, in which case it must have been discontinued at least 3 months before study entry; patients who were pregnant or nursing; use of other agents for treatment of hot flashes for at least 2 weeks before study entry; prior thromboembolic disease; uncontrolled hypertension	37.5 mg/day for 1 week, followed by 75 mg/day for 5 weeks	Improved hot flash scores
Carpenter JS, Stornio AM, Johns S, <i>et al.</i> <sup>15)</sup>	randomized, double-blind, placebo-controlled, crossover	70	12 weeks	adult women with a history of breast cancer; no other cancer; disease-free and functioning independently at the time of study enrollment; at least 4 weeks removed from completing local therapy; daily hot flashes; desire of treatment for hot flashes but not currently using any other hot flash treatments; postmenopausal or using a clinically acceptable method of birth control throughout the study to prevent pregnancy; living within 60 miles of the study site to enable access to the hot flash monitor; verified as being nondepressed	tamoxifen or aromatase inhibitor use for <6 weeks; antidepressant user; receiving hot flash treatment within the past 4 weeks; pregnant or lactating	37.5 or 75 mg/day	Decreased hot flash frequency

**Table 1. Summary of clinical studies of venlafaxine for the treatment of hot flashes (continued)**

Loibl S, Schwedler K, von Minckwitz G, <i>et al.</i> <sup>16)</sup>	double-blind, randomized, crossover	80	8 weeks	age older than 18 years with primary breast cancer; troublesome hot flashes, occurring at least 14 times per week for at least 1 month or desire of treatment for hot flashes; performance status of 0–1 on the Eastern Cooperative Oncology Group scale	previous treatment with venlafaxine and clonidine as well as estrogens, progestogens, or androgens for hot flashes; current treatment with hypertensive or antidepressant agents, other non-hormonal agents for hot flashes; patients with hypertension or hypotension, peripheral or cardiovascular diseases, or symptomatic cardiac diseases; metastatic disease	37.5 mg twice a day	Improved hot flash scores; decreased hot flash frequency
Buijs C, Mom CH, Willemse PH, <i>et al.</i> <sup>17)</sup>	double-blind, randomized, crossover	60	18 weeks	women with primary or metastatic breast cancer; aged 60 years; hot flashes, occurring at least 14 times per week; adequate liver and kidney functions; a life expectancy of 6 months; performance status of 0–1 on the Eastern Cooperative Oncology Group scale	previous use of venlafaxine or clonidine; had received other treatment for hot flashes within the previous month; had treated with a $\beta$ -blocker, sedatives or antidepressants.	75 mg/day	Improved hot flash scores
Irani J, Salomon L, Oba R, <i>et al.</i> <sup>18)</sup>	double-blind, randomized	311	10 weeks	men with prostatic adenocarcinoma who could not have received any hormonal therapy	treated with drugs related to the study medications or that were potentially effective for the treatment of hot flashes; contraindications to any of the study drugs; diabetes, severe kidney, liver, and cardiovascular disease; psychiatric progressive disease; a history of thromboembolism	75 mg/day	Improved hot flash scores
Walker EM, Rodriguez AI, Kohn B, <i>et al.</i> <sup>19)</sup>	randomized, controlled	50	12 weeks	stage 0-III pre- or postmenopausal breast cancer patients on hormone therapy with tamoxifen or arimidex; age older than 18 years; hot flashes, occurring at least 14 times per week; may have been treated locally with surgery and/or radiation and must have completed chemotherapy; may be receiving radiation therapy but otherwise must be within 5 years after treatment; must be on a stable dose of hormone therapy for 4 weeks or more without plans to discontinue therapy for the duration of the study; Karnosky performance status (KPS) >70; life expectancy >6 months	not applicable	37.5 mg/day for 1 week, followed by 75 mg/day for 11 weeks	Decreased hot flash frequency

tatic adenocarcinoma who could not have received any hormonal therapy. Researchers randomized patients to one of three treatments: venlafaxine 75 mg/day (n=102), medroxyprogesterone 20 mg/day (n=108), or cyproterone acetate 100 mg/day (n=101). All participants received two indistinguishable pills in the morning and one in the evening from week 1 to week 8, and then one in the morning and one in the evening from week 9 to week 10. This method made this study comply with the double-blind design considering the gradual discontinuation of venlafaxine (given at half-dose, 37.5 mg/day in weeks 9 and 10). After 4 weeks of treatment, the median hot flash scores decreased significantly from baseline in all three treatment groups ( $p < 0.0001$ ). The change was -47.2% in the venlafaxine group, -94.5% in the cyproterone group, and -83.7% in the medroxyprogesterone group. The change in the median hot flash scores from baseline to 8 weeks and to the last available score was -56.7% and -57.1%, respectively in the venlafaxine group. Gastrointestinal disorders such as nausea and constipation were the most common adverse effects observed in the venlafaxine group, and there was no significant difference between the three treatment groups in terms of adverse effects. The study population was men in this study, which is different than the other studies reviewed in this paper.

Walker EM, Rodriguez AI, Kohn B, et al. assessed the effect of venlafaxine on hot flashes in breast cancer patients.<sup>19)</sup> Patients should have hot flashes, occurring at least 14 times per week for enrollment in this 12-week, randomized, controlled study. Participants were randomized to receive either venlafaxine (n=25) or acupuncture (n=25). In the venlafaxine group, patients took venlafaxine 37.5 mg/day for 1 week, followed by 75 mg/day for 11 weeks. Both groups showed a significant reduction (50%) in the hot flash frequency from baseline to post-treatment ( $p < 0.05$ ). Patients in the venlafaxine group reported nausea, dry mouth, dizziness, and anxiety as adverse effects, while there was no adverse effects occurred in the acupuncture group. This study only included patients with breast cancer, and sample size was small. Therefore, it's difficult to apply

the results to general population.

## SUMMARY

The results from eight randomized controlled studies demonstrate that venlafaxine is effective in the treatment of hot flashes with tolerable adverse effects.<sup>12-19)</sup> Based on the results of the above studies, venlafaxine can be recommended for the treatment of hot flashes. However, there are limitations in the above studies. The inclusion criteria of 5 studies reviewed in this paper was breast cancer patients, so it's hard to apply the results to the general population in clinical practice. Also 5 studies had less than 100 subjects included, and 18-week study was the longest one among studies reviewed in this paper. Therefore, large and long-term clinical studies with the general population should be conducted to use venlafaxine for the treatment of hot flashes in clinical practice.

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