

Citalopram과 Escitalopram의 안면홍조 증상개선효과에 대한 최근 연구 고찰

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(2011년 8월 8일 접수 · 2011년 9월 26일 수정 · 2011년 9월 27일 승인)

Citalopram and Escitalopram for Management of Hot Flashes: A Review of Recent Clinical Trials in Humans

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(Received August 8, 2011 · Revised September 26, 2011 · Accepted September 27, 2011)

폐경기는 여성들에게 신체적, 정신적으로 많은 변화 및 불편함을 야기시킨다. 특히 안면홍조는 폐경기 초기 많은 여성들에게 나타나는 증상이며 혈중 에스트로겐 수치가 낮아졌을 때 나타나기 때문에 현재까지 에스트로겐을 기본으로 한 호르몬 요법이 안면홍조 증상의 1차 치료제로 여겨졌다. 그러나 2002년 호르몬 요법이 유방암, 뇌졸중 등의 발생 위험도를 증가시킨다는 연구 결과가 발표된 이후 많은 보건의료인들은 호르몬 요법 대신 사용 가능한 다른 치료제의 등장을 고대하고 있다. 안면홍조 증상을 지닌 많은 폐경기 여성들 또한 호르몬 요법 대신 안전하게 사용할 수 있는 효과적인 치료제를 기다리고 있다. 현재 citalopram과 escitalopram은 안면홍조 증상 치료제로 허가된 의약품은 아니지만 최근 여러 국가에서 시행된 연구들은 citalopram과 escitalopram이 효과적인 안면홍조 증상 치료제일 수 있다는 가능성을 보여주고 있다. 따라서 본 연구는 citalopram과 escitalopram의 안면홍조 증상 치료효과에 대한 최신 지견을 얻고자, 1990년부터 2011년 1월까지 MEDLINE에 등재된 논문을 Citalopram 또는 Escitalopram과 Hot flashes라는 MeSH terms로 검색하여 추출한 자료 중에서 임상연구 사례만을 선별하여 임상적 유용성을 평가하였다.

□ Key words - citalopram, escitalopram, hot flashes, menopause

INTRODUCTION

For many women, menopause is a emotionally and physically struggling experience in their life. Hot flashes, fatigue, depression, anxiety, night sweats, and insomnia have been reported in women during menopausal periods.¹⁾ Of these, hot flashes are the major sign of menopause and the most troubling symptom of women during the perimenopausal and early menopausal years. Hot flashes are usually characterized by a sudden sensation of heat or burning starting on the face and neck area that rapidly passes over the entire body. It is generally accepted that estrogens play a main role

in etiology of hot flashes because women experience hot flashes when their blood estrogen levels are low or after bilateral oophorectomy. Therefore, hormone replacement therapy with estrogen has been the first-line treatment for hot flashes with high efficacy for many years. In 2002, the Women's Health Initiative study showed that the rates of breast cancer, coronary artery disease, stroke, and pulmonary embolism in women with estrogen-progestin increased compared to placebo.²⁻⁴⁾ Now many health care professionals do not want to use hormonal therapies for hot flashes because of the results of the Women's Health Initiative study. Moreover, a randomized study from Sweden Hormone Replacement Therapy after Breast Cancer Diagnosis - Is It Safe? (HABITS) was stopped because an increased risk of breast cancer was observed in patients receiving hormonal replacement therapy as compared to those with-

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out hormonal replacement therapy in 2003.⁵⁾ So many women want to take nonhormonal medications to help them manage hot flashes. The physiology of hot flashes has not been fully understood, but prostaglandins, serotonin, histamine, and substance P are suggested as the mediators of hot flashes.⁶⁻⁷⁾ Antidepressant therapy has become a crucial area of investigation for treatment of hot flashes due to the potential interaction between serotonin and estrogen.⁷⁻¹¹⁾ The purpose of this study is to assess the effect of citalopram and escitalopram on hot flashes by reviewing published clinical studies. A MEDLINE search (from January 1990 to January 2011) was conducted using a combination search term citalopram or escitalopram and hot flashes with limits of clinical trial, humans, and English.

CITALOPRAM AND ESCITALOPRAM

Citalopram and escitalopram have indications for the treatment of major depressive disorder. The chemical names for citalopram and escitalopram are 1-[3-(Dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalanarbonitrile and 1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-*S*-(+)-5-isobenzofurancarbonitrile oxalate, respectively.¹²⁻¹³⁾ Citalopram has a potent and highly selective inhibiting activity of serotonin reuptake and its effect on other neurotransmitters such as dopamine or norepinephrine is minimal. Escitalopram is the *S*-enantiomer of the racemic derivative citalopram, and it is also selective inhibitor of serotonin reuptake with minimal effect on norepinephrine or dopamine reuptake.¹⁴⁻¹⁵⁾ Since citalopram and escitalopram are highly lipophilic, these are absorbed rapidly from the GI tract, reaching maximum plasma concentrations about 4 hours after oral administration. Metabolism of these two medications is extensively hepatic, and cytochrome P-450 (CYP) 3A4 and 2C19 isoenzymes are the main enzymes involved in the metabolism.¹⁶⁻¹⁹⁾

Literature Review

Barton DL *et al.* conducted a 4-week, open-label study to assess the efficacy of citalopram for the treatment of hot flashes in women.²⁰⁾ Women who had a

history of breast cancer or who were fearful of developing breast cancer from estrogen use were included. They must have had hot flashes for at least 1 month and have hot flashes, occurring at least 14 times per week for enrollment. They were excluded if they had been on any antidepressant in the past year. A total of 21 participants were instructed to take citalopram 10 mg daily for 1 week, followed by 20 mg daily for 3 weeks. During the study period, 6 subjects stopped taking citalopram due to its toxicities such as rash, hives, trouble sleeping, and bladder spasm. Three out of these 6 subjects submitted evaluable data as did other participants who completed the study. After the 4 weeks of citalopram use, hot flash scores decreased 64% from baseline and hot flash frequencies also decreased by 58%. There was no significant increases in nausea, dizziness, constipation, nervousness, or depression over the study duration. There are limitations in this study. First, this study was not a placebo-controlled trial. Second, the treatment period of this study was short, and participants were primarily breast cancer survivors. Therefore, placebo-controlled, longer studies with the general population should be conducted to use citalopram for the treatment of hot flashes in clinical practice.

A 9-month, randomized, double-blind, placebo-controlled study was conducted to test citalopram, fluoxetine, or placebo in 150 healthy women with distressing menopausal symptoms.²¹⁾ Participants were randomly assigned to one of three groups: citalopram, fluoxetine, or placebo. The doses of both citalopram and fluoxetine were 10 mg daily for 1 month, followed by 20 mg daily for 5 months, then 30 mg daily for 3 months. There was significant improvement in mean number of hot flashes and Kupperman Index (KI) scores from baseline in all three groups ($p < 0.001$). However, no significant differences were observed among the three groups in mean number of hot flashes and KI scores. At 9 months, discontinuation rates were 40%, 34%, and 34% in the placebo, fluoxetine, and citalopram group, respectively. Treatment period of this study was relatively longer compared to other studies reviewed in this paper. That the inclusion criteria was not breast cancer patients was also different than

the first study reviewed here.

Loprinzi CL *et al.* conducted a 4-week, open-label study to evaluate the effect of citalopram on hot flashes.²²⁾ Women who had a history of breast cancer or who were fearful of developing breast cancer from estrogen use were included. They should have experience of insufficient hot flashes control with venlafaxine and had to have distressing hot flashes (≥ 14 times per week) for at least 1 month prior to study entry. Participants received citalopram 10 mg daily for 1 week, followed by 20 mg daily for 3 weeks. Twenty-two out of 30 participants completed the entire protocol and returned evaluable information. After 4 weeks of the treatment period, hot flash scores decreased by 53% and mean hot flash frequencies also decreased by 45% compared with baseline ($p < 0.001$). The study medication, citalopram was well tolerated. Since this study was an open-label trial, it was not possible to identify the true efficacy associated with citalopram as a treatment for hot flashes compared to placebo. Sample size was small and the duration of active treatment was also short in this study.

Another 8-week, open-label study tested escitalopram as treatment for hot flashes.²³⁾ To be eligible for this study, women had to be perimenopausal and postmenopausal with depressive disorders and menopausal symptoms. They were aged 40 to 60 years. Participants were randomly assigned to receive either escitalopram 10 mg daily or ethinyl estradiol 5 mcg daily plus norethindrone acetate 1 mg daily. Treatment with escitalopram was initiated at 10 mg daily for 4 weeks, with dosing further adjusted up to 20 mg daily. The primary outcome of this study was depression improvement measured by changes in the Montgomery-Asberg Depression Rating Scale (MADRS). Menopausal symptoms were assessed using the Greene Climacteric Scale (GCS), providing scores of psychological, physical, and vasomotor symptoms. The difference in GCS total scores with escitalopram (median decrease=17.8) compared to ethinyl estradiol plus norethindrone acetate (median decrease=8.75) was statistically significant ($p=0.01$). There were similar changes in the subscores of vasomotor symptoms in patients

with escitalopram to those with ethinyl estradiol plus norethindrone acetate. This study was not a placebo-controlled trial. Sample size was small and the duration of study was also short.

In an 8-week, randomized, placebo-controlled trial, Kalay AE *et al.* assessed citalopram as treatment for hot flashes in healthy, menopausal women.²⁴⁾ Eligible subjects should have at least 7 hot flashes per day. A total of 100 participants were randomly assigned to receive one of four treatments: citalopram, placebo, citalopram plus hormone therapy, and placebo plus hormone therapy. The dose of citalopram was 10 mg daily for the first week, then increased to 20 mg daily for 3 weeks. For the next 4 weeks, the citalopram dose could be increased to 40 mg daily in cases where response was not sufficient. The mean hot flash scores decreased significantly in all groups compared with baseline ($p < 0.01$). The reduction rates were 37% in the citalopram group, 13% in the placebo group, 50% in citalopram plus hormone therapy group, and 14% in placebo plus hormone therapy group. There was significantly greater improvement in reducing hot flashes with the citalopram and citalopram plus hormone therapy than with placebo or placebo plus hormone therapy ($p < 0.01$). The mean Kupperman index significantly decreased from baseline in all groups ($p = 0.005$), but it was improved significantly more in the citalopram group and citalopram plus hormone therapy group compared with the placebo group or placebo plus hormone therapy group ($p = 0.001$). Somnolence ($n = 7$), increased perspiration ($n = 2$), palpitation ($n = 2$), and dry mouth ($n = 1$) were reported adverse effects of citalopram. The strength of this study is that the participants were healthy, primarily naturally menopausal women. Short study duration is the limitation of this study.

An 8-week, single-blind, placebo lead-in study was conducted to assess the efficacy of escitalopram for hot flashes.²⁵⁾ This study enrolled 25 natural menopausal women without depression, and they had to have more than 14 hot flashes per week. Since previous hot flash studies showed the high rates of placebo response, eligible women received a placebo for 1 week, then subjects who were decided to be placebo responders were

Table 1. Summary of clinical studies of citalopram and escitalopram for the treatment of hot flashes

Author	Study Design	Number of Subjects	Study Duration	Inclusion Criteria	Exclusion Criteria	Medication and Dose	Outcomes
Barton DL <i>et al.</i> ²⁰⁾	Open-label	18	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 and for at least 1 month; life expectancy at least 6 months; performance status of 0–1 on the Eastern Cooperative Oncology Group scale	Any antidepressant treatment in the past year; use of other medications to treat hot flashes within the previous 2 weeks	Citalopram, 10 mg/day for 1 week, followed by 20 mg/day for 3 weeks	Improved hot flash scores; decreased hot flash frequency
Suvanto-Luukkonen E <i>et al.</i> ²¹⁾	Randomized, double-blind, placebo-controlled	150	9 months	Natural menopause; at least 6 months amenorrhoea; serum FSH levels above 30 IU/L; seeking relief from menopausal symptoms	Surgical menopause; metal illness; use of psychopharmaceutical drugs; history of malignant disease	Citalopram, 10 mg/day for 1 month, followed by 20 mg/day for 5 months, then 30 mg/day for 3 months	Improved mean number of hot flashes and Kupperman Index (KI) scores from baseline (p<0.001)
Loprinzi CL <i>et al.</i> ²²⁾	Open-label	22	4 weeks	Women with a history of breast cancer or fear of getting breast cancer from estrogen use; failed venlafaxine therapy for hot flashes; troublesome hot flashes, occurring at least 14 times per week and for at least 1 month; life expectancy at least 6 months	Treatment with antineoplastic chemotherapy, androgens, progestational agents, clonidine, or gabapentin; use of antidepressant except venlafaxine; history of clinical depression; history of an allergic or adverse reaction to citalopram	Citalopram, 10 mg/day for 1 week, followed by 20 mg/day for 3 weeks	Improved hot flash scores; decreased hot flash frequency (p<0.001)
Soares <i>et al.</i> ²³⁾	Open-label	32	8 weeks	Perimenopausal and postmenopausal women, who presented with depressive disorders and menopause-related symptoms; aged 40 to 60 years	Clinical contraindications to estrogen therapy, such as hypersensitivity to conjugated estrogens, medroxyprogesterone acetate, or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or thromboembolic disorders; carcinoma of the breast; estrogen-dependent tumors; hepatic dysfunction or disease	Escitalopram, 10 mg/day for 4 weeks, may adjust up to 20 mg/day for the next 4 weeks	Decreased GCS (Greene Climacteric Scale) total scores with escitalopram compared to estrogen plus progestogen therapy (p=0.01)
Kalay AE <i>et al.</i> ²⁴⁾	Randomized, placebo-controlled	100	8 weeks	Natural or surgical menopause; more than seven to eight hot flashes per day; normal thyroid function	Current psychotic disease; use of psychiatric therapy; use of herbal products, dopaminergic or antidopaminergic drugs, or narcotic analgesics	Citalopram, 10 mg/day for 1 week, followed by 20 mg/day for 3 weeks, may increase to 40 mg/day for 4 weeks	Improved mean hot flash scores and Kupperman Index (KI) scores from baseline (p<0.05)
Defronzo Dobkin R <i>et al.</i> ²⁵⁾	Single blind placebo lead-in	22	8 weeks	Menopausal women; at least 14 hot flashes per week; natural cessation of menstrual periods for at least 12 months; no current psychiatric diagnosis; absent or minimal levels of depressive symptoms	Hormone replacement therapy within the past 6 months; prior history of poor response to hormone replacement therapy; history of breast or other types of cancer; any current, medically unstable condition; history of substance abuse or dependence within the past year; lifetime history of major depressive disorder, suicide attempts, or self injurious behavior; initiation of psychotherapy within the past 3 months; any major sleep disturbances	Escitalopram, 10 mg/day for 4 weeks, may adjust up to 20 mg/day for the next 4 weeks	Improved hot flash frequency and severity

Table 1. Summary of clinical studies of citalopram and escitalopram for the treatment of hot flashes (continued)

Barton DL <i>et al.</i> ²⁶⁾	Randomized, double-blind, placebo-controlled	196	6 weeks	Postmenopausal women; at least 14 hot flashes per week for at least the past month	Use of any antineoplastic therapy, estrogen, or testosterone; evidence of active malignancy; use of other treatments for hot flashes; use of other antidepressants	Citalopram, 10, 20, and 30 mg/day	Improved hot flash scores; decreased hot flash frequency; no significant differences among doses
Freeman EW <i>et al.</i> ²⁷⁾	Randomized, double-blind, placebo-controlled	194	8 weeks	Aged 40 to 62 years; menopause transition (amenorrhea 60 days in the past year), or postmenopausal (12 months since last menstrual period or bilateral oophorectomy), or had a hysterectomy with 1 or both ovaries remaining and follicle-stimulating hormone levels higher than 20 mIU/mL and estradiol of 50 pg/mL or less; at least 28 hot flashes or night sweats per week for 3 weeks; hot flashes or night sweats rated as bothersome or severe on 4 or more days per week; the frequency in week 3 did not decrease by more than 50% from the mean weekly levels in weeks 1 and 2	Use of psychotropic medications, prescription, over-the-counter, or herbal therapies for hot flashes in the past 30 days; hormone therapy, hormonal contraceptives, selective estrogen receptor modulators (SERMs), or aromatase inhibitors in the past 2 months; current severe medical illness; major depressive episode; drug or alcohol abuse in the past year; suicide attempt in the past 3 years; lifetime diagnosis of bipolar disorder, or psychosis; uncontrolled hypertension; history of endometrial or ovarian cancer; myocardial infarction, angina or cerebrovascular events; other preexisting medical conditions	Escitalopram, 10 mg/day for 4 weeks, may adjust up to 20 mg/day for the next 4 weeks	Improved hot flash frequency and severity ($p < 0.001$)

excluded from the escitalopram treatment trial. There was no placebo responder and 22 participants completed this study. Three subjects stopped the study because of adverse effects of escitalopram such as anxiety and insomnia. The dose of escitalopram was 10 mg daily for 4 weeks and further adjusted up to 20 mg daily for the next 4 weeks. There were significant decreases in hot flash frequencies. Sixteen subjects were treatment responders with greater than 50% decrease in hot flash frequency. The limitation of this study includes a small sample size and uncontrolled study design.

Barton DL *et al.* conducted a 6-week, double-blind, placebo-controlled, randomized study to evaluate the efficacy of citalopram for hot flashes in postmenopausal women.²⁶⁾ Subjects should have hot flashes, occurring at least 14 times per week to be eligible in this study. Researchers randomized participants to one of three groups: citalopram 10 mg daily versus placebo, citalopram 20 mg daily versus placebo, or citalopram 30 mg daily versus placebo. In each group, subjects receiving

active agents compared to those with placebo were decided in a 2:1 ratio. All participants received their assigned dose starting with one pill (10 mg versus placebo) and increasing by one pill per week (10 versus placebo) until target dose was attained. The maximum dose was three pills (30 mg versus placebo) daily. After 6 weeks of the study duration, daily hot flash scores decreased significantly from baseline by 7.0 with citalopram 10 mg daily, 7.7 with 20 mg daily, 10.7 with 30 mg daily, and 2.0 with placebo ($p \leq 0.002$). Hot flash frequencies were also significantly reduced by 3.6, 3.9, 4.5, and 1.4 with 10 mg daily, 20 mg daily, 30 mg daily and placebo, respectively ($p < 0.001$). No significant difference was observed in the change in hot flash scores or frequencies with any doses of citalopram. Citalopram was well tolerated without significant adverse effects. That this study tested whether there was any difference in hot flash reduction between doses of citalopram is the strength of this study. However, the duration of this study was short.

Freeman EW *et al.* assessed the effect of escitalopram on hot flashes in women aged 40 - 62 years, who were either in the menopause transition or postmenopausal.²⁷⁾ Participants should have more than 28 hot flashes per week, occurring for at least 4 days per week for enrollment in this 8-week, multicenter, randomized, double-blind, placebo-controlled trial. Participants were randomized to receive either escitalopram or placebo. In the escitalopram group, subjects took escitalopram 10 mg daily for 4 weeks. After 4 weeks, if the decrease in hot flash frequency was not attained by at least 50% with no severity reduction, the dose was doubled for the next 4 weeks. At week 8, the mean change of hot flash frequency reduction (number of hot flashes per day) was 1.41 (95% CI, 0.13-2.69) with escitalopram ($p < 0.001$). The mean decrease was 4.6 events (47%) per day with escitalopram compared to 3.2 events (33%) per day with placebo. There were significantly more reductions in hot flash severity scores with escitalopram compared to placebo (-0.52; 95% CI, -0.64 to -0.40 versus -0.30; 95% CI, -0.42 to -0.17; $p < 0.001$). Investigators also evaluated whether there were racial differences in response to escitalopram for hot flashes, but no significant effect was observed ($p = 0.62$). Subjects in the escitalopram group reported nausea, vivid dreams, dizziness, lightheadedness, and excessive sweating as adverse effects, but there was no serious adverse effects requiring medical intervention or study withdrawal. This study is the only clinical trial evaluating the effects of race on the response to escitalopram.

SUMMARY

The results from eight clinical studies demonstrate that citalopram and escitalopram could be an effective option in the treatment of hot flashes with tolerable adverse effects.²⁰⁻²⁷⁾ However, there are limitations in the above studies. The inclusion criteria of 2 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 4 studies had less than 50 subjects included, and the duration of study was 8 weeks or

less in 7 studies reviewed in this paper. Moreover, only 4 studies were randomized, placebo-controlled trials (3 for citalopram and 1 for escitalopram). Therefore, further randomized, double-blind, placebo-controlled studies with the general population should be needed to use citalopram and escitalopram for the treatment of hot flashes in clinical practice.

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