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Efficacy of Continuous Transdermal Nitroglycerin for Treating Hot Flashes by Inducing Nitrate Cross-tolerance in Perimenopausal and Postmenopausal Women
A Randomized Clinical Trial

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IMPORTANCE Due to the potential risks of long-term systemic estrogen therapy, many menopausal women are interested in nonhormonal treatments for vasomotor symptoms. Physiologic studies indicate that nitric oxide plays a key role in mediating hot flash–related vasodilation, suggesting that nonhormonal medications that induce nitrate tolerance in the vasculature may offer therapeutic benefit for vasomotor symptoms.

OBJECTIVE To determine whether uninterrupted administration of transdermal nitroglycerin (NTG) to induce nitrate cross-tolerance decreased the frequency or severity of menopause-related hot flashes.

DESIGN, SETTING, AND PARTICIPANTS This randomized, double-blinded, placebo-controlled clinical trial included perimenopausal or postmenopausal women reporting 7 or more hot flashes per day who were recruited from northern California by study personnel at a single academic center. Patients were randomized between July 2017 and December 2021, and the trial ended in April 2022 when the last randomized participant completed follow-up.

INTERVENTIONS Uninterrupted daily use of transdermal NTG (participant-directed dose titration from 0.2-0.6 mg/h) or identical placebo patches.

MAIN OUTCOME MEASURES Validated symptom diaries assessing changes in any hot flash frequency (primary outcome) and moderate-to-severe hot flash frequency over 5 and 12 weeks.

RESULTS Among the 141 randomized participants (70 NTG [49.6%], 71 placebo [50.4%]; 12 [85.8%] Asian, 16 [11.3%] Black or African American, 15 [10.6%] Hispanic or Latina, 3 [2.1%] multiracial, 1 [0.7%] Native Hawaiian or Pacific Islander, and 100 [70.9%] White or Caucasian individuals), a mean (SD) of 10.8 (3.5) hot flashes and 8.4 (3.6) moderate-to-severe hot flashes daily was reported at baseline. Sixty-five participants assigned to NTG (92.9%) and 69 assigned to placebo (97.2%) completed 12-week follow-up (P = .27). Over 5 weeks, the estimated change in any hot flash frequency associated with NTG vs placebo was −0.9 (95% CI, −2.1 to 0.3) episodes per day (P = .10), and change in moderate-to-severe hot flash frequency with NTG vs placebo was −1.1 (95% CI, −2.2 to 0) episodes per day (P = .05). At 12 weeks, treatment with NTG did not significantly decrease the frequency of any hot flashes (−0.1 episodes per day; 95% CI, −1.2 to 0.4) or moderate-to-severe hot flashes (−0.5 episodes per day; 95% CI, −1.6 to 0.7) relative to placebo. In analyses combining 5-week and 12-week data, no significant differences in change in the frequency of any hot flashes (−0.5 episodes per day; 95% CI, −1.6 to 0.6; P = .25) or moderate-to-severe hot flashes (−0.8 episodes per day; 95% CI, −1.9 to 0.2; P = .12) were detected with NTG vs placebo. At 1 week, 47 NTG (67.1%) and 4 placebo participants (5.6%) reported headache (P < .001), but only 1 participant in each group reported headache at 12 weeks.

CONCLUSIONS AND RELEVANCE This randomized clinical trial found that continuous use of NTG did not result in sustained improvements in hot flash frequency or severity relative to placebo and was associated with more early but not persistent headache.

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Visual Abstract

Supplemental content

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Hot flashes (vasomotor symptoms) are among the most common symptoms of menopause, with more tan two-thirds of women in Western nations reporting hot flashes during the menopausal transition.[1-3] Although hormone therapy is effective in suppressing these symptoms, prolonged use of systemic estrogen after menopause has been reported to increase risk of estrogen-sensitive cancers, thromboembolic disease, stroke, and dementia.[4-6] As a result, many women are interested in nonhormonal treatments that are effective but pose fewer long-term health risks.

Recent efforts to identify alternative hot flash treatments have focused on central nervous system (CNS) mechanisms that are hypothesized to play a role in triggering these symptoms, such as changes in the thermoregulatory set point of the hypothalamus.[7,8] However, to our knowledge, few nonhormonal medications directed at CNS mechanisms have been found effective,[9-11] and none yet appear as potent as estrogen therapy. Further, although CNS mechanisms are implicated in the pathophysiology of hot flashes, the direct physical manifestation of the hot flash is peripheral vasodilation, resulting in flushing, sweating, and the sensation of heat over the head, chest, and arms. As a result, mechanisms underlying peripheral vasodilation may offer a more direct target for hot flash treatment.

Clinical laboratory-based studies have indicated that nitric oxide (NO) plays a central role in mediating vasodilation during hot flashes, with local cutaneous blockade of NO synthase suppressing hot flash–related vasodilation.[12-14] One pharmacologic agent with direct and potent effects on NO-mediated vasodilation is nitroglycerin (NTG, or 1, 2, 3-propanetriol, trinitrate), an organic nitrate widely used to treat chest pain in patients with coronary disease by promoting coronary vasodilation. While intermittent use of NTG triggers release of NO, promotes vascular smooth muscle relaxation, and triggers vasodilation, sustained NTG use rapidly leads to tolerance to the drug's vasodilatory effects within only 24 hours, as well as cross-tolerance to endogenous nitrates as a result of enhanced NO degradation.[15-20] This phenomenon, widely known as nitrate tolerance, offers a potential approach to decreasing vasomotor symptoms by suppressing NO-mediated peripheral vasodilation.[21]

The goal of the Flushing Reduction Associated With Nitrates (FRAN) study was to evaluate the effects of continuous transdermal NTG on menopause-related hot flash frequency and severity. In addition to evaluating continuous NTG as a clinical treatment approach, we aimed to obtain clinical confirmatory evidence of the physiologic role of NO-specific vasodilation in mediating the physical manifestations of the hot flash.

Key Points

Question Does uninterrupted transdermal nitroglycerin therapy decrease the frequency and severity of menopause-related hot flashes?

Findings In this randomized clinical trial that included 141 perimenopausal and postmenopausal women who experienced at least 7 hot flashes per day, hot flash frequency decreased by more than 40% over 12 weeks in the nitroglycerin and placebo groups. Early reductions in moderate-to-severe hot flash frequency or hot flash severity scores associated with nitroglycerin at 5 weeks did not persist at 12 weeks relative to placebo.

Meaning This randomized clinical trial found that continuous use of transdermal nitroglycerin does not result in sustained improvements in hot flash frequency or severity relative to placebo.

Methods

Design and Participants

FRAN was the first randomized, parallel-group, double-blinded, placebo-controlled, 12-week trial of uninterrupted transdermal NTG therapy (Supplement 1). Participants were women aged 40 to 62 years recruited from the general San Francisco Bay Area by personnel affiliated with the University of California San Francisco. To be eligible, women had to be in the late menopausal transition, which was defined by amenorrhea for at least 60 days in the past 12 months, or postmenopausal, which was defined by (1) history of bilateral oophorectomy, (2) follicle-stimulating hormone levels more than 20 mU/mL in the setting of hysterectomy without bilateral oophorectomy, or (3) self-reported amenorrhea for at least 12 months in the absence of hysterectomy or bilateral oophorectomy. Candidates also had to have experienced 7 or more hot flashes per day (24 hours) and 4 or more moderate-to-severe hot flashes per day documented on a validated 7-day screening symptom diary.

Candidates were ineligible if they reported use of NTG or other nitrate-containing medications during the past 4 weeks; vaginal estrogen or progestins during the past 4 weeks or systemic estrogen during the past 12 weeks; other medications with potential efficacy for hot flashes (clonidine, methyldopa, gabapentin, pregabalin, or selective serotonin or norepinephrine reuptake inhibitors) during the past 4 weeks; or medications that posed a safety risk with coadministration of NTG (eg, phosphodiesterase inhibitor medications) during the past 4 weeks. Other exclusions included self-reported history of hypertrophic obstructive cardiomyopathy, aortic valve stenosis, or mitral valve stenosis; self-reported history of coronary disease, diabetes, or 2 or more major risk factors for coronary disease (due to potential increased risk of coronary events with continuous NTG use); evidence of prior myocardial infarction, second-degree or third-degree atrioventricular block, or uncontrolled tachyarrhythmias on screening electrocardiogram; resting blood pressure less than 90/60 or more than 180/110 mm Hg or orthostatic hypotension at baseline; preexisting history of headaches requiring prescription medication (which could be worsened by NTG); recent pregnancy or breastfeeding or plans to become pregnant; self-reported heavy alcohol use (>7 drinks per week); or a known allergy or sensitivity to nitrates or to skin adhesives. All participants provided written informed consent as approved by the University of California San Francisco institutional review board.

Randomization, Interventions, and Blinding

Eligible participants were randomly assigned in a fixed 1:1 ratio to uninterrupted self-administration of transdermal NTG vs placebo daily for 12 weeks. Randomization was performed by computer in permuted blocks of 2 and 4 stratified by menopausal status (postmenopausal vs late menopausal transition). An independent contracted statistician prepared the allocation sequence and provided it to the research pharmacy preparing study medication (Clinical Trial Services). Nitroglycerin and identical placebo patches were prepared by the research pharmacy for distribution to participants. Participants, investigators, and study staff were masked to treatment assignment, and no unmasking occurred during the trial.

Before randomization, each candidate completed a brief run-in period during which they applied a 0.1-mg/h NTG patch daily for 3 days. At baseline, candidates who successfully completed the run-in were allowed to proceed with the treatment phase. Those unable to tolerate the run-in patch or who developed resting or orthostatic hypotension were ineligible.

During the treatment phase, participants self-administered generic transdermal NTG patches (Mylan Pharmaceuticals) to provide continuous and controlled release of NTG at dosages that ranged from 0.2 to 0.6 mg/h daily or identical-appearing placebo patches designed by the research pharmacy. Participants were instructed to apply a new patch each night directly after removing the old one. Adherence was assessed using medication diaries in which participants affixed their used patch to the diary after removal.

To enable participant-directed dose titration, all participants initially self-administered a 0.2-mg/h patch (NTG or placebo, per randomization assignment) at baseline. At 1 and 2 weeks, participants who reported persistent hot flashes, did not have blood pressure lower than 90/60 or higher than 180/110 mm Hg, and reported no other major safety or tolerability issue were invited to increase their dose to 0.4 and then 0.6 mg/h (NTG or placebo). Participants who reported being completely satisfied with a dose lower than 0.6 mg/h or who developed safety or tolerability issues continued to take a lower dose. At the 12-week visit, participants were asked to gradually discontinue NTG use over 1 to 3 days.

Outcomes and Measurements

The primary outcome of repeated change in frequency of any hot flashes over 5 and 12 weeks was assessed using a validated 7-day symptom diary[22-24] in which participants recorded each hot flash they experienced and rated its severity on a 3-point scale: (1) mild (sensation of heat without sweating), (2) moderate (sensation of heat with sweating that did not prevent the participant from continuing with activity), or (3) severe (sensation of heat with sweating, which caused cessation of activity). To avoid diary fatigue, participants were asked to complete the diary for a 7-day period at baseline, 5 weeks (initiated at 4 weeks), and 12 weeks (initiated at 11 weeks) only. Secondary outcomes included change in average diary-reported frequency of moderate-to-severe hot flashes over 7 days and a diary-derived total hot flash severity score calculated as the sum of severity ratings for all hot flashes recorded over 7 days. Additional secondary outcomes in this report included changes in the Hot Flash Related Daily Interference Scale score, a 10-item self-administered questionnaire that assesses the degree to which hot flashes interfered with respondents' activities during the prior week,[25] and the 3-item vasomotor domain of the Menopause-Specific Quality of Life questionnaire that assesses condition-specific quality of life impact.[7,26]

To monitor safety, study coordinators systematically queried participants about potentially severe adverse effects of NTG therapy at each follow-up assessment after initiation of treatment with NTG or placebo: (1) headache severe enough to interfere with instrumental activities of daily living; (2) chest tightness or pain interfering with instrumental activities of daily living, and (3) syncope. Resting blood pressure measurements were obtained at baseline, 1 week, 5 weeks, and 12 weeks. Other unanticipated adverse events were assessed by asking participants about any negative changes in their health at each follow-up contact.

Statistical Analyses and Power

The sample size was based on parameter estimates from prior pharmacologic hot flash trials,[8,27] assuming (1) a mean baseline frequency of any hot flashes of more than 9 episodes per day; (2) mean reduction in any hot flash frequency in the placebo group of fewer than 3 episodes per day; (3) standard deviation of change in hot flash frequency of approximately 4.5 episodes per day; and (4) correlation between baseline and follow-up values of approximately 0.55. Within these assumptions, a sample size of 140 (70 per group) was selected to provide more than 85% power in 2-sided tests, with a type 1 error of 5% to detect a 20% greater reduction in hot flash frequency (or 1.8 episodes per day) in the NTG vs placebo arm.[28]

The baseline characteristics of participants in each treatment group were compared using Wilcoxon, Mann-Whitney *U*, and Fisher exact tests as appropriate. Linear mixed models were then developed to examine repeated changes in hot flash frequency and severity outcomes after initiation of treatment. The approximate normality of the residuals was verified using density plots, and sensitivity to the slight departures we detected was ruled out using models with robust standard errors.

The primary protocol-specified treatment effect analysis was based on linear mixed models for the repeated changes assessed over 5 and 12 weeks (based on 7-day diaries initiated after 4 and 11 weeks of therapy), which were adjusted for baseline values and any participant characteristics unevenly distributed, assuming approximately constant treatment effects over time. However, separate protocol-specified models that examined separate time-specific treatment effects after 5 weeks and 12 weeks were also created. All analyses were conducted according to treatment assignments, without regard to treatment adherence, following an intention-to-treat approach. Subgroup analyses were planned only if test results for interaction with age, menopausal stage, body mass index, and use of estrogen receptor modulators were significant at $P < .05$.

Additional protocol-specified sensitivity analyses were performed to address potential bias arising from missing data through attrition or nonresponse. Missing imputation analy-

ses were performed for all participants with intent to treat[29] without making assumptions about adherence. Twenty multiply-imputed data sets were created using the Markov chain Monte Carlo method, including demographic characteristics, treatment assignment, and interim outcomes. Summary effect estimates and standard errors were computed by standard methods for imputed data.

Safety analyses compared the rates of adverse events and abnormal blood pressure measurements between groups using Fisher exact tests. All analyses were performed with SAS (version 9.4; SAS Institute).

Results

Recruitment, Retention, and Adherence

Between July 2017 and December 2021, 70 participants were randomized to receive treatment with NTG and 71 to placebo (**Figure**). All participants took at least 1 dose of assigned medication or placebo. Fourteen assigned to receive NTG (19.7%) and 5 assigned to placebo (7.1%) discontinued treatment before 12 weeks (P = .06). The trial ended in April 2022 when the last randomized participant completed follow-up.

At baseline, the mean (SD) participant age was 53.9 (3.8) years in the placebo and 55.3 (3.9) years in the NTG group (P = .04) (**Table 1**). More participants in the NTG vs placebo group reported Black race (17.1% vs 5.6%; P = .051 for overall racial heterogeneity).

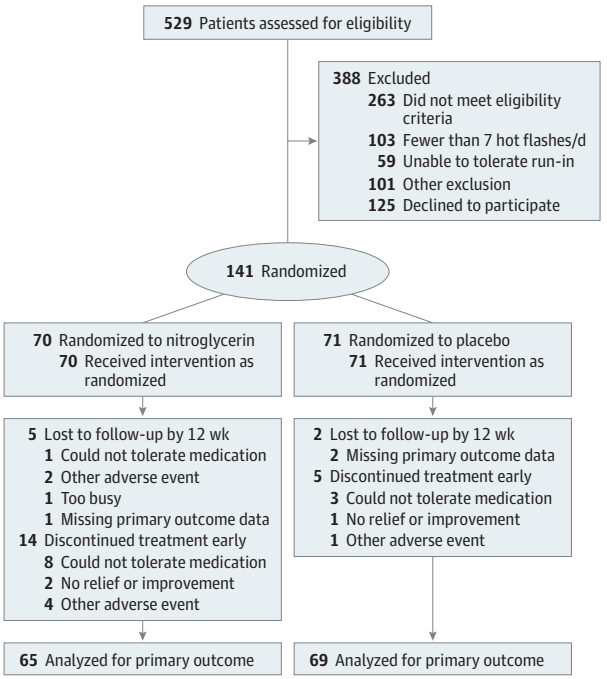
At baseline, participants reported a mean (SD) of 10.8 (3.5) hot flashes and 8.4 (3.6) moderate-to-severe hot flashes daily, without significant between-group differences (Table 1). Follow-up hot flash frequency and severity data were available for 65 participants assigned to receive NTG and 70 to placebo at 5 weeks and 65 assigned to receive NTG and 69 to placebo at 12 weeks (P = .27). Compared with those with complete 12-week data, more participants missing 12-week data self-identified as Hispanic or Latina (25.0% vs 8.3%; P = .04; eTable 1 in Supplement 2).

Among participants who did not discontinue the study medication early, 61 (96.8%) assigned to receive NTG and 67 (95.7%) to placebo were at least 75% adherent to medication (P > .99) at 5 weeks; at 12 weeks, 55 (93.2%) assigned to receive NTG and 65 (97.0%) assigned to placebo were at least 75% adherent to medication (P = .67). By 5 weeks, 37 (58.7%) of the participants retained in the NTG group were using the highest dose of NTG (0.6 mg/h) (eTable 2 in Supplement 2); by 12 weeks, 29 (49.2%) were using highest-dose NTG. After 12 weeks, 39 participants (27.7%) in the NTG and 38 (27.0%) in the placebo group correctly guessed their treatment assignment (P = .45), indicating successful maintenance of blinding.

Hot Flash Outcomes

Over 5 weeks, the average frequency of any hot flashes decreased by 4.5 episodes per day in the NTG group vs 3.6 episodes per day in the placebo group for an estimated between-group difference of −0.9 episodes per day (95% CI, −2.1 to 0.3; P = .10); moderate-to-severe hot flash frequency decreased by

Figure. CONSORT Diagram



Recruitment, randomization, and retention.

3.3 episodes per day in the NTG vs 2.2 episodes per day in the placebo group for a between-group difference of −1.1 episodes per day (95% CI, −2.2 to 0; P = .05) (**Table 2**). By 12 weeks, average reductions in the frequency of any hot flashes were similar across groups (between-group difference of −0.1 episodes per day; 95% CI, −1.2 to 1.4; P = .85), as were reductions in the frequency of moderate-to-severe hot flashes (between-group difference of −0.5 episodes per day; 95% CI, −1.6 to 0.7; P = .43) (Table 2). Similarly, no significant between-group differences in change in other hot flash outcomes, such as total hot flash severity score, Hot Flash Related Daily Interference Scale score, or Menopause Quality of Life vasomotor score, were detected over 12 weeks (Table 2).

In primary outcome models that combined 5-week and 12-week outcomes data, and after adjusting for participant age, race, and ethnicity as characteristics distributed differentially at baseline or associated with loss-to-follow-up, NTG therapy resulted in an average decrease of 4.5 hot flash episodes per day vs 4.0 episodes per day with placebo (estimated between-group difference of −0.5 episodes per day; 95% CI, −1.6 to 0.6; P = .35). The average frequency of moderate-to-severe hot flashes in the combined 5-week and 12-week models decreased by 3.3 episodes per day in the NTG and 2.5 episodes per day in the placebo group (between-group difference of −0.8 episodes per day; 95% CI, −1.9 to 0.2; P = .12) (**Table 3**). Similarly, no significant between-group differences in change in other hot flash outcomes were detected in these combined models.

Supplementary protocol-specified analyses incorporating multiple imputation of missing data yielded similar results (eTable 3 in Supplement 2), although estimated between-

Table 1. Baseline Characteristics of Randomized Participants by Treatment Assignment

Characteristic	Nitroglycerin (n = 70)	Placebo (n = 71)	Standardized mean difference
Age, mean (SD), y	55.3 (3.9)	53.9 (3.8)	.36
Race, No. (%)			
Asian	4 (5.7)	8 (11.3)	−0.20
Black or African American	12 (17.1)	4 (5.6)	0.36
Multiracial	0	3 (4.2)	NA
Native Hawaiian or Pacific Islander	1 (1.4)	0	NA
White or Caucasian	50 (71.4)	50 (70.4)	.02
Other or unknown	3 (4.3)	6 (8.5)	−0.17
Hispanic or Latina ethnicity	8 (11.4)	7 (9.9)	0.05
Menopausal history, No. (%)			
Status post bilateral oophorectomy	4 (5.7)	5 (7.0)	−0.05
Status post hysterectomy	9 (12.9)	10 (14.1)	−0.04
Nonsurgically postmenopausal	57 (81.4)	55 (77.5)	0.10
Late menopausal transition	13 (18.6)	16 (22.5)	−0.10
Medications, No. (%)			
Aromatase inhibitor	2 (2.9)	1 (1.4)	0.10
Selective estrogen receptor modulator	2 (2.9)	0	NA
Hot flash frequency/severity, mean (SD)			
Hot flashes per day	10.8 (4.0)	10.9 (2.9)	−0.04
Moderate-to-severe hot flashes per day	8.7 (4.1)	8.1 (3.0)	0.16
Total diary-based hot flash severity score	21.1 (9.1)	20.4 (6.0)	0.26
Hot flash–related quality of life, mean (SD)			
Menopause-specific quality of life vasomotor domain score	6.5 (1.4)	6.2 (1.4)	0.20
Hot flash–related daily interference scale score	46.1 (23.1)	40.3 (21.0)	0.26

Abbreviation: NA, not applicable.

Table 2. Time-Specific Change in Hot Flash Frequency and Severity Outcomes by Treatment Assignment

Characteristic	Mean change (95% CI)[a]			*P* value
	Nitroglycerin (n = 65)	Placebo (n = 71)	Between-group difference	
Change from baseline to 5 wk of treatment				
Average No. of hot flashes per day	−4.5 (−6.0 to −3.1)	−3.6 (−5.0 to −2.2)	−0.9 (−2.1 to 0.3)	.14
Average No. of moderate-to-severe hot flashes per day	−3.3 (−4.7 to −1.9)	−2.2 (−3.5 to −0.8)	−1.1 (−2.2 to 0.0)	.05
Total daily diary-based hot flash severity score	−8.3 (−11.4 to −5.1)	−6.1 (−9.1 to −3.1)	−2.2 (−4.7 to 0.4)	.09
Hot flash–related daily interference scale score	−20.2 (−29.2 to −11.2)	−18.1 (−26.6 to −9.5)	−2.1 (−9.5 to 5.3)	.56
Menopause-specific quality of life vasomotor domain score	−1.5 (−2.3 to 0.6)	1.3 (−2.1 to 0.4)	−0.2 (−0.1 to 0.5)	.54
Change from baseline to 12 wk of treatment				
Average No. of hot flashes per day	−4.6 (−6.1 to −3.1)	−4.7 (−6.2 to −3.3)	−0.1 (−1.2 to 1.4)	.85
Average No. of moderate-to-severe hot flashes per day	−3.3 (−4.7 to −1.9)	−2.8 (−4.1 to −1.5)	−0.5 (−1.6 to 0.7)	.43
Total daily diary-based hot flash severity score	−8.4 (−11.6 to −5.3)	−8.1 (−11.2 to −5.1)	−0.3 (−3.0 to 2.3)	.81
Hot flash–related daily interference scale score	−20.0 (−28.5 to −11.1)	−22.3 (−30.7 to −13.9)	2.5 (−4.6 to 9.6)	.49
Menopausal quality of life vasomotor domain score	−1.6 (−2.5 to 0.7)	−1.4 (−2.3 to 0.5)	−0.2 (−0.9 to 0.6)	.60

[a] Estimates of mean change and 95% CIs were derived from linear mixed models, adjusted for baseline values, as well as participant age, race, and ethnicity as characteristics distributed differentially at baseline, or associated with loss to follow-up.

group differences in the reduction in moderate-to-severe hot flash frequency were more pronounced in these models. Specifically, NTG therapy was associated with 1.2 (95% CI, 2.2-0.06) fewer moderate-to-severe hot flashes per day than placebo (P = .04) in models that combined 5-week and 12-week data and imputing missing data.

Table 3. Overall Change in Hot Flash Frequency and Severity Outcomes From Baseline to 5 and 12 Weeks of Treatment by Treatment Assignment

Characteristic	Mean change (95% CI)[a]			P value
	Nitroglycerin (n = 65)	Placebo (n = 71)	Between-group difference	
Average No. of hot flashes per day	−4.5 (−6.0 to −3.1)	−4.0 (−5.4 to −2.6)	−0.5 (−1.6 to 0.6)	.35
Average No. of moderate-to-severe hot flashes per day	−3.3 (−4.6 to −1.9)	−2.5 (−3.7 to −1.2)	−0.8 (−1.9 to 0.2)	.12
Total daily diary-based hot flash severity score	−8.4 (−11.4 to −5.3)	−6.9 (−9.9 to −4.0)	−1.4 (−3.8 to 1.0)	.24
Hot flash–related daily interference scale score	−20.0 (−28.5 to −11.5)	−20.5 (−28.6 to −12.3)	0.4 (−6.2 to 7.1)	.90
Menopause-specific quality of life vasomotor domain score	−1.5 (−2.4 to −0.6)	−1.33 (−2.2 to −0.5)	−0.2 (−0.9 to −0.5)	.57

[a] Estimates of mean change and 95% CIs were derived from linear mixed models, adjusted for baseline values, as well as participant age, race, and ethnicity as characteristics distributed differentially at baseline, or associated with loss to follow-up.

Table 4. Adverse Events and Abnormal Blood Pressure Measurements After Treatment Initiation by Treatment Assignment[a]

Characteristic	Nitroglycerin, No. (%) (n = 70)	Placebo, No. (%) (n = 71)	P value[b]
Participant-reported adverse events[a]			
Any adverse event	65 (92.9)	66 (93.0)	>.99
Headache	60 (85.7)	58 (81.7)	.65
Headache at 1 wk	46 (65.7)	4 (5.6)	<.001
Headache at 12 wk	1 (1.4)	1 (1.4)	>.99
Headache interfering with instrumental activities of daily living	12 (17.1)	8 (11.3)	.23
Chest pain or tightness interfering with instrumental activities of daily living	3 (4.3)	0	.12
Syncope, fainting, or loss of consciousness	1 (1.4)	0	.50
Resting blood pressure abnormalities			
Systolic pressure <90 or diastolic pressure <60 mm Hg	1 (1.4)	0	.50
Systolic pressure >160 or diastolic pressure >100 mm Hg	2 (2.9)	0	.25

[a] Adverse events were reportable through 1 week after discontinuation of study medication.

[b] *P* values for between-group differences in event rates were calculated by Fischer exact tests.

Treatment effects on the frequency of moderate-to-severe hot flashes were also examined in subgroups defined by menopause stage, following protocol-specified interaction testing that indicated that treatment-associated changes in this outcome differed for women in the late menopausal transition vs postmenopausal women. Among participants in the late menopausal transition, moderate-to-severe hot flash frequency decreased by 3.0 greater episodes per day in the NTG vs placebo group (95% CI, −5.2 to −0.2; *P* = .01); among postmenopausal participants, reductions in moderate-to-severe hot flash frequency did not differ substantially for the NTG group vs placebo (−0.3 episodes per day; 95% CI, −1.4 to 0.8; *P* = .59; eTable 4 in Supplement 2). No significant treatment interactions were detected for age, body mass index, or use of estrogen receptor modulators.

Safety Outcomes

One week after initiation of study medication, 47 (67.1%) of participants assigned to NTG and 4 (5.6%) assigned to placebo reported headache (*P* < .001), but only 1 in each group reported headache at 12 weeks (**Table 4**). Three participants assigned to receive NTG reported self-limited episodes of chest pain or tightness and 1 had a syncopal episode; none assigned to placebo reported chest pain or tightness of syncope. Rates of low systolic (<90 mm Hg) or diastolic (<60 mm Hg) blood pressure did not differ between the groups (Table 4).

Discussion

In this randomized double-blinded clinical trial, uninterrupted transdermal NTG therapy did not result in sustained overall reductions in frequency of any hot flashes relative to placebo over 12 weeks, despite initially greater reductions in moderate-to-severe hot flash frequency with NTG therapy at 5 weeks, as well as greater improvements in moderate-to-severe hot flash frequency with NTG therapy in models that imputed missing data over 5 and 12 weeks. Although prior research has indicated that hot flash–related vasodilation is mediated by NO mechanisms that could be suppressed by inducing nitrate tolerance,[12-14] this trial's findings do not support a recommendation to use transdermal NTG as a clinical treatment for hot flashes.

The more than 40% reductions in hot flash frequency or severity in the NTG group at 5 weeks were sustained at 12 weeks, but the more modest reductions in hot flashes in the placebo group observed at 5 weeks became more pronounced by 12 weeks, eroding early between-group differ-

ences. It is possible that continuous NTG therapy was initially more efficacious in suppressing hot flashes, but participants assigned to the placebo group experienced progressive, natural resolution of their hot flashes (ie, greater reversion to the mean) over time. Alternately, early treatment benefits associated with NTG could have plateaued if sustained administration of NTG eventually brought about compensatory increases in alternate peripheral vasodilation mechanisms independent of NO. Subgroup analysis results also raise the possibility that NTG therapy could offer greater benefits for highly symptomatic women in the immediate menopausal transition rather than those with persistent hot flashes after menopause. However, the conservative assumption is that any observed trend toward greater reduction in moderate-to-severe hot flashes at 5 weeks or in any subgroup occurred by random chance.

Initial study plans assumed only a 33% decrease in any hot flash frequency in the placebo group, compared with the more than 40% average decrease that was subsequently observed in the placebo group over 12 weeks. Although substantial placebo effects have been observed in several recent hot flash treatment trials,[30] trial plans were informed by earlier research suggesting lower placebo effects in trials of nonhormonal hot flash therapies.[31]

As anticipated, NTG therapy was associated with a greater prevalence of headache at 1 week than placebo. However, by 12 weeks, headache was not more prevalent in the NTG group, with only 1 participant taking NTG reporting headache. These findings suggest that uninterrupted NTG therapy was effective in inducing and maintaining nitrate tolerance because participants gradually ceased to experience headache that was attributable to NTG-related vasodilation.

Limitations

The limitations of this study included the higher rate of early medication discontinuation in the NTG group (19.7%), although most participants who discontinued medication use still provided hot flash outcomes data. Additionally, the trial relied on an only 1-week screening period to determine candidates' baseline hot flash frequency and severity rather than confirming that symptom burden remained high for multiple weeks before enrollment. This could partially explain the greater-than-expected improvement in hot flashes in the placebo group, with many participants demonstrating regression to the mean after enrollment.

Conclusions

Overall, the findings of this trial do not support daily uninterrupted use of transdermal NTG as a nonhormonal treatment for menopause-associated vasomotor symptoms. Further research could explore other approaches to inducing nitrate tolerance or evaluate other physiologic mechanisms aside from NO-mediated vasodilation underlying the peripheral manifestations of the hot flash.

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