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Article

ARTICLE

Oxybutynin vs Placebo for Hot Flashes in Women With or Without Breast Cancer: A Randomized, Double-Blind Clinical Trial (ACCRU SC-1603)

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Abstract

Background: Hot flashes (HFs) negatively affect quality of life among perimenopausal and postmenopausal women. This study investigated the efficacy of oxybutynin vs placebo in decreasing HFs.
Methods: In this randomized, multicenter, double-blind study, women with and without breast cancer with 28 or more HFs per week, lasting longer than 30 days, who were not candidates for estrogen-based therapy, were assigned to oral oxybutynin (2.5 mg twice a day or 5 mg twice a day) or placebo for 6 weeks. The primary endpoint was the intrapatient change from baseline in weekly HF score between each oxybutynin dose and placebo using a repeated-measures mixed model. Secondary endpoints included changes in weekly HF frequency, HF-related daily interference scale questionnaires, and self-reported symptoms.
Results: We enrolled 150 women. Baseline characteristics were well balanced. Mean (SD) age was 57 (8.2) years. Two-thirds (65%) were taking tamoxifen or an aromatase inhibitor. Patients on both oxybutynin doses reported greater reductions in the weekly HF score (5 mg twice a day: −16.9 [SD 15.6], 2.5 mg twice a day: −10.6 [SD 7.7]), placebo −5.7 (SD 10.2); $P < .005$ for both oxybutynin doses vs placebo), HF frequency (5 mg twice a day: −7.5 [SD 6.6], 2.5 mg twice a day: −4.8 [SD 3.2], placebo: −2.6 [SD 4.3]; $P < .003$ for both oxybutynin doses vs placebo), and improvement in most HF-related daily interference scale measures and in overall quality of life. Patients on both oxybutynin arms reported more side effects than patients on placebo, particularly dry mouth, difficulty urinating, and abdominal pain. Most side effects were grade 1 or 2. There were no differences in study discontinuation because of adverse effects.
Conclusion: Oxybutynin is an effective and relatively well-tolerated treatment option for women with HFs.

Hot flashes (HFs) occur in about 75% of women at midlife, interfering with many spheres of life and overall quality of life (QoL) (1,2). Breast cancer survivors are at higher risk for long-term and more severe HFs as a consequence of chemotherapy-induced menopause, ovarian function suppression, and the use of tamoxifen or aromatase inhibitors (3). Development of HFs can be associated with premature discontinuation of adjuvant endocrine therapy and lead to worse breast cancer outcomes (4–6).

The most established treatment for HFs is estrogen-based therapy (7); however, it is usually avoided in women with a history of, or at increased risk for, breast cancer. Several randomized trials have identified non estrogen medications that are effective for HFs treatment, such as serotonin reuptake

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inhibitors, serotonin-norepinephrine reuptake inhibitors (8–21), and anticonvulsants (10,22–27). Unfortunately, these may not be effective for all women, and they may have limiting side effects, and/or women may be reluctant to take them. Moreover, some antidepressants inhibit CYP2D6, which has been associated with decreased tamoxifen efficacy (28), although data on this are mixed (29). Therefore, additional nonestrogen treatment options for women with breast cancer and HFs are needed.

Although the pathophysiology of HFs is not fully understood, multiple neurotransmitters have been implicated, including norepinephrine, serotonin, and acetylcholine (30–32). Oxybutynin is an anticholinergic drug approved by the US Food and Drug Administration for treatment of overactive bladder symptoms. Decreased sweating is a common side effect of oxybutynin, which has led to its successful use in the treatment of generalized hyperhidrosis (33). Anecdotal and retrospective data suggest that oxybutynin could also be effective in the treatment of refractory HFs (34). In a prospective, double-blind, clinical trial evaluating an extended-release formulation of oxybutynin for HFs, at a dose of 15 mg daily, patients experienced significant reductions in the frequency and severity of HFs at 12 weeks (35). Unfortunately, this dose was associated with excess toxicity and treatment discontinuation because of side effects.

The present trial evaluated the hypothesis that oxybutynin, at lower doses of 2.5 mg twice a day (Oxy2.5) or 5 mg twice a day (Oxy5), would be more effective than placebo in treating HFs and in improving QoL with an acceptable toxicity profile.

Patients and Methods

Participants

In this randomized, double-blind, placebo-controlled clinical trial, we recruited premenopausal and postmenopausal women with HFs from 10 centers in the United States, all members of the Academic and Community Cancer Research United Network. Eligible patients were adult women who, over a period greater than 30 days, experienced 28 or more HFs per week of sufficient severity to prompt them to seek treatment. Patients with or without a history of breast cancer were eligible, as long as they did not have evidence of active disease. Additional inclusion criteria were: Eastern Cooperative Oncology Group performance status of 0–1 and the ability of the participant to provide informed written consent and to complete study questionnaires.

Patients were excluded if they were receiving cytotoxic chemotherapy, estrogen, progestogens, androgens, or potent anticholinergics. Human epidermal growth factor receptor 2 (HER2)–directed therapy was allowed. Ongoing treatment with tamoxifen, raloxifene, or an aromatase inhibitor was allowed, as long as the dose had been stable for at least 28 days and there was a plan to continue treatment during the study period. Additional exclusion criteria were prior use of oxybutynin (during the period in which the patient experienced HFs), pregnancy, breastfeeding, or contraindications to the use of oxybutynin.

Written informed consent was obtained from each participant, and the study protocol was reviewed and approved by the appropriate local institutional review boards of each study center.

Random Assignment and Masking

Women were randomly assigned to receive either 2.5 or 5 mL twice a day of a liquid, oral formulation containing 2.5 mg oxybutynin/placebo or 5 mg oxybutynin/placebo, resulting in a 2:1 chance of receiving oxybutynin, compared with placebo. Web-based randomization was used, using the Pocock and Simon dynamic allocation procedure (36). Stratification factors included age (18–49 years vs 50 years or older), concurrent tamoxifen use, concurrent aromatase inhibitor use, HF duration (<9 vs >9 months), and average baseline HFs frequency per day (4–9 vs ≥ 10).

Procedures

During the first week of the study, no medication was administered, and questionnaires (HF diary, a symptom experience questionnaire, and the Hot Flash Related Daily Interference Scale (HFRDIS)) were completed to establish baseline symptoms. Following this, patients received their assigned treatment for 6 weeks. All patients started at a dose of 2.5 mL twice a day (2.5 mg oxybutynin/placebo) and received their target dose on the second week. Patients continued to complete a daily HF diary and a weekly symptom experience questionnaire during their 6 weeks on the study and the HFRDIS at the end of the study.

Outcomes

The primary endpoint was the intrapatient change from baseline to 6 weeks in the weekly HF score. HFs were measured by a prospective, self-reported HF diary (37). The daily HF score (37) (a composite of both frequency and severity) was computed by multiplying the frequency of each HF grade by the severity of the HF (grade 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe) and subsequently summing all of the numbers.

Secondary endpoints included change from baseline of HF frequency; change from baseline of daily HF interference between oxybutynin and placebo, as measured by the HFRDIS (39), summarized by descriptive statistics, and then compared using Wilcoxon rank sum tests or two sample t-tests; and adverse effects, evaluated using the National Cancer Institute Common Terminology for Adverse Events (CTCAE) version 4.0, as well as a weekly self-reported symptom experience questionnaire. The HFRDIS and adverse effects were rated on a 0- to 10-point scale, where 0 is as bad as it can be and 10 is as good as it can be.

Statistical Analysis

Sample-size calculations were based on a time-averaged repeated-measures model, comparing oxybutynin to placebo. Model assumptions include a moderate correlation of 0.5 between repeated HF scores and a minimal meaningful difference in changes from the baseline of half an SD, which is considered a moderate effect size and clinically meaningful (39). Using a two-sided 5% significance level, 42 patients per arm were required to provide 85% power to detect this half SD effect size. Accrual goals were adjusted for an expected dropout rate of 15%, resulting in an accrual goal of 50 patients per arm.

The time-averaged intrapatient changes in HF activity from baseline during the treatment period were compared between treatment and placebo arms using a repeated-measures mixed model of weekly HF scores and frequency. Patient baseline characteristics, including age, concurrent use of tamoxifen or

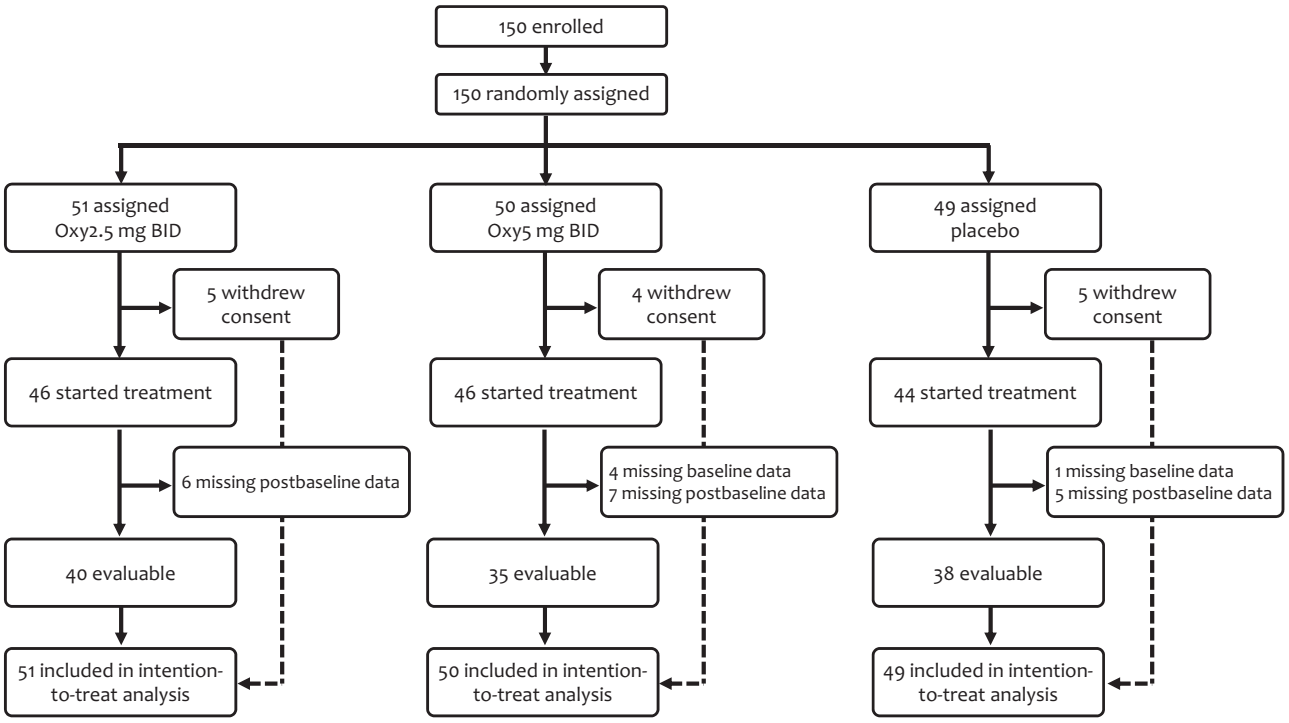

Figure 1. Consolidated Standards of Reporting Trials diagram. Oxy = oxybutynin.

aromatase inhibitor, and baseline HF duration and frequency, were used as covariates in the model. Estimates from this model were used to construct a 95% confidence interval (CI) for the mean difference in intrapatient change of HFs between the treatment and placebo arms. Sensitivity analyses, using 10 different methods of imputing missing values, were conducted to provide evidence that missing data did not unduly influence the results of the study.

Because the two treatment arms represented different doses of the same drug, a fixed sequence of up to two hypotheses tests was performed, rather than two simultaneous tests, as would generally be done for studies in which the primary analysis involves two independent hypotheses. This is based on the belief that the treatment effect of oxybutynin, if one existed, would change monotonically with respect to dose. To control the overall type-I error for the primary analysis, a gatekeeping procedure, a method recommended by the Food and Drug Administration and the National Cancer Institute for adjusting for multiple testing (40), was employed. In particular, a time-averaged longitudinal model to test the higher-dose oxybutynin arm vs placebo was first used at the level 0.05, using a two-sided alternative. Plans to test the lower-dose oxybutynin arm vs placebo was to be carried out only if the higher-dose arm–vs-placebo test was statistically significant, again at the level 0.05 and using a two-sided alternative.

An intention-to-treat analysis (ITT) was also performed to account for missing data. For this analysis, we chose as endpoints the percentage of patients who reported a 50% or greater reduction from baseline in their HF score and HF frequency during the study period. Both oxybutynin doses were compared against placebo using the Fisher exact test. Additionally, a logistic regression model was used, adjusting for age, concomitant tamoxifen or aromatase inhibitor use, baseline HF duration, and baseline number of HFs per day. In all ITT analyses, patients with missing values were assumed to not have a 50% or greater reduction from baseline in either HF score or frequency.

This study was registered in Clinicaltrials.gov as NCT02961790.

Results

In total, 150 women were accrued between February 23, 2017, and March 5, 2018. A Consolidated Standards of Reporting Trials diagram is illustrated in Figure 1. Of the 150 patients randomly assigned, 14 (9%) withdrew consent before treatment initiation, and 23 (15%) did not submit either baseline or postbaseline questionnaires, leaving 113 patients evaluable for the primary endpoint. Mean (SD) patient age was 57 (8.2) years. Baseline characteristics were well balanced and are detailed in Table 1. Seventy-three evaluable patients (65%) were receiving active endocrine therapy for breast cancer, either tamoxifen or an aromatase inhibitor, during the conduct of the study.

Patients on each of the oxybutynin arms, compared with those on placebo, achieved greater reductions in both HF score and HF frequency (Figure 2 and Table 2). The observed reduction in HF score was −16.9 (SD 15.6) with Oxy5, −10.6 (SD 7.7) with Oxy2.5, and −5.7 (SD 10.2) with placebo ($P < .005$ for both oxybutynin doses vs placebo). The observed reduction in HF frequency was −7.5 (SD 6.6) with Oxy5, −4.8 (SD 3.2) with Oxy 2.5, and −2.6 (SD 4.3) with placebo ($P < .003$ for both oxybutynin doses vs placebo). This was confirmed with repeated-measures mixed models, adjusting for baseline variables ($P < .001$). A decrease in the HF score was seen as early as 1 week after initiation of oxybutynin, and it reached the maximum decrease after 4 weeks with both doses (Figure 2).

In addition to the effect on HF score and frequency, patients on Oxy5 had larger improvements in most of the HFRDIS interference measures, including work, social activities, leisure

Table 1. Baseline characteristics (N = 113)*

Variable	Placebo (n = 38) No. (%)	2.5 mg twice a day (n = 40) No. (%)	5 mg twice a day (n = 35) No. (%)
Mean (SD) age, y	58.2 (8.4)	55.6 (8.0)	57.6 (8.4)
Age group			
18–49	6 (15.8)	9 (22.5)	6 (17.1)
>49	32 (84.2)	31 (77.5)	29 (82.9)
Concurrent treatment			
Concurrent AI	13 (34.2)	15 (37.5)	11 (31.4)
Concurrent tamoxifen	12 (31.6)	9 (22.5)	13 (37.1)
HF frequency at enrollment, HF/day			
4-9	22 (57.9)	20 (50.0)	19 (54.3)
≥10	16 (42.1)	20 (50.0)	16 (45.7)
HF duration, months			
<9	7 (18.4)	9 (22.5)	8 (22.9)
≥9	31 (81.6)	31 (77.5)	27 (77.7)
Average (SD) HF score per day during baseline week	19.7 (12.2)	15.6 (9.7)	19.5 (17.4)
Average (SD) HF frequency during baseline week, HF/day	9.6 (5.3)	8.0 (4.3)	9.7 (7.6)

*AI = aromatase inhibitor; HF = hot flash.

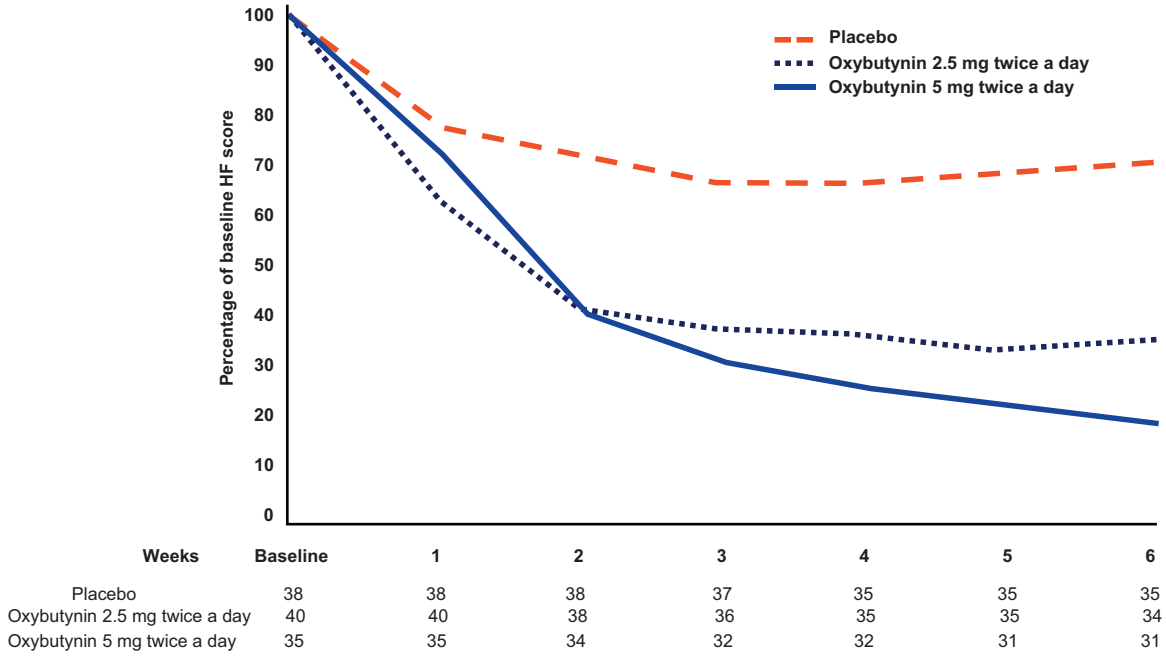

Figure 2. Mean hot flash (HF) score percentage of baseline. Numbers under each week of treatment represent the number of evaluable patients at each week.

activities, sleep, mood, relationships, life enjoyment, and overall QoL ($P < .008$ for all, Table 3). The only interference measures not improved by Oxy5 were concentration and sexuality. Similarly, most interference measures were statistically significantly improved with Oxy2.5, with the exception of concentration, sexuality, mood, and life enjoyment. Self-reported satisfaction with HF control and improvement in HF distress were higher with Oxy5 vs placebo ($P = .002$ and .005, respectively), but not with Oxy2.5 vs placebo ($P = .669$ and .066, respectively).

To evaluate whether study results could have been influenced by the missing data on 37 patients, an ITT analysis including data for all 150 randomly assigned patients was conducted. Thirteen patients (26.5%) on placebo reported a 50% or greater reduction in HF score, compared with 26 patients (51%) on Oxy2.5 ($P = .015$) and 30 patients (60%) on Oxy5 ($P = .001$). Similarly, 10 patients (20.4%) on placebo reported a 50% or greater reduction in HF frequency, compared with 25 patients (49%) on Oxy2.5 ($P = .003$) and 28 patients (56%) on Oxy5 ($P < .001$). These differences remained after adjusting for baseline factors using a logistic regression model. Patients on either oxybutynin dose were more likely than patients on placebo to have a 50% or greater reduction in HF score (OR = 3.2, 95% CI = 1.3 to 7.7 for Oxy2.5 vs placebo; OR = 5.8, 95% CI = 2.2 to 15.2 for Oxy5 vs placebo).

Oxybutynin was well tolerated at both doses. When assessing symptoms as reported by study staff using CTCAE 4.0, dry

Table 2. Reductions in hot flash (HF) score and frequency from baseline to week 6

HF measure	Placebo (n = 38)	Oxy2.5 (n = 40)	P*	Oxy5 (n = 35)	P†	P‡
HF score						
Mean (SD) reduction	5.7 (10.2)	10.6 (7.7)	.004	16.9 (15.6)	< .001	.0368
Percentage reduction	29%	70%		86%		
HF frequency						
Mean (SD) reduction	2.6 (4.3)	4.8 (3.2)	.002	7.5 (6.6)	< .001	.0355
Percentage reduction	27%	60%		77%		

*Placebo vs oxybutynin 2.5 mg twice a day.
†Placebo vs oxybutynin 5 mg twice a day.
‡Oxybutynin 2.5 mg twice a day vs oxybutynin 5 mg twice a day.

Table 3. Changes in hot flash daily interference scales from baseline to week 6

	Placebo (n = 38)		2.5 mg twice a day (n = 40)			5 mg twice a day (n = 35)			
Interference measure*	Mean	SD	Mean	SD	P (placebo vs Oxy2.5)	Mean	SD	P (placebo vs Oxy5)	P (Oxy2.5 vs Oxy5)
Work	0.2	3.2	−2.9	3.2	.001	−2.3	3.4	.003	.754
Social activities	−0.1	3.4	−2.3	2.8	.005	−2.6	2.8	.002	.823
Leisure activities	−0.5	3.0	−2.5	2.5	.007	−3.1	2.5	<.001	.323
Sleep	−1.2	3.7	−3.7	3.0	.003	−4.9	3.7	<.001	.141
Mood	−1.3	3.6	−2.3	2.6	.092	−3.4	2.5	.007	.076
Concentration	−1.1	3.0	−1.9	2.5	.301	−2.2	2.2	.115	.398
Relationships	0.0	2.3	−1.9	2.6	.013	−2.4	2.3	<.001	.189
Sexuality	−0.4	3.4	−2.3	3.2	.064	−2.4	3.3	.06	.987
Life enjoyment	−1.0	2.8	−2.1	2.7	.052	−3.1	2.8	.005	.256
Overall quality of life	−0.5	3.2	−2.5	2.8	.009	−3.2	2.7	<.001	.471

*Interference scores run from 0 to 10, with 0 being no interference, and 10 being complete interference. Changes reported are comparing end of study (week 6 of treatment) to baseline. A negative value indicates improvement, whereas a positive value indicates interference is worse than at baseline.

Table 4. Changes in self-reported adverse events from baseline to week 6

	Placebo (n = 38)		2.5 mg twice a day (n = 40)			5 mg twice a day (n = 35)			
Symptom*	Mean	SD	Mean	SD	P (placebo vs Oxy2.5)	Mean	SD	P (placebo vs Oxy5)	P (Oxy2.5 vs Oxy5)
Dry mouth	−0.1	2.1	1.9	3.0	.003	2.9	3.4	.001	.268
Difficulty urinating	−0.1	1.3	0.5	1.6	.048	0.9	1.8	.002	.245
Constipation	−0.9	1.8	−0.2	1.4	.057	0.3	2.1	.004	.186
Abdominal pain	−1.4	2.5	−0.3	1.5	.017	0.0	1.3	.028	.861
Vomiting	−0.2	1.0	0.0	0.2	.086	0.0	0.2	.091	.949
Decrease in appetite	−0.6	2.1	−0.1	0.8	.995	0.6	2.2	.115	.090
Rash	0.1	0.5	0.5	1.9	.612	0.0	1.4	.204	.173
Dry eyes	−0.6	2.5	0.8	2.1	.025	0.2	1.9	.281	.250
Insomnia	−2.0	3.2	−1.8	2.4	.780	−2.5	3.2	.369	.346
Diarrhea	−0.7	1.9	0.5	1.6	.004	−0.8	2.5	.456	.020
Episodes of confusion	−0.4	1.2	0.2	1.0	.031	−0.1	0.8	.469	.163
Nausea	−1.1	2.3	−0.2	0.7	.122	−0.7	1.8	.521	.430
Blurry vision	−0.4	1.7	0.2	1.1	.211	0.1	1.4	.646	.563
Headaches	−1.1	2.5	−0.3	1.8	.049	−1.3	2.6	.699	.147
Difficulty concentrating	−1.1	2.1	−0.4	1.2	.099	−1.0	2.3	.723	.246
Dizziness	−0.6	2.3	0.0	1.6	.464	−0.1	1.9	.754	.754
Myalgias or arthralgias	−0.9	2.7	−0.6	1.7	.824	−1.0	2.2	.757	.758
Excessive somnolence	−0.4	2.4	−0.3	1.7	.842	−0.5	1.7	.874	.940
Urinary incontinence	−0.4	1.2	−0.3	1.1	.537	−0.4	1.4	.955	.539
Fatigue	−1.7	3.0	−0.6	1.9	.197	−1.7	2.4	.980	.163

*Symptoms were scored from 0 to 10, with higher values representing higher severity. Changes reported are comparing end of study (week 6 of treatment) to baseline. A negative value indicates improvement, whereas a positive value indicates the symptom is worse than at baseline.

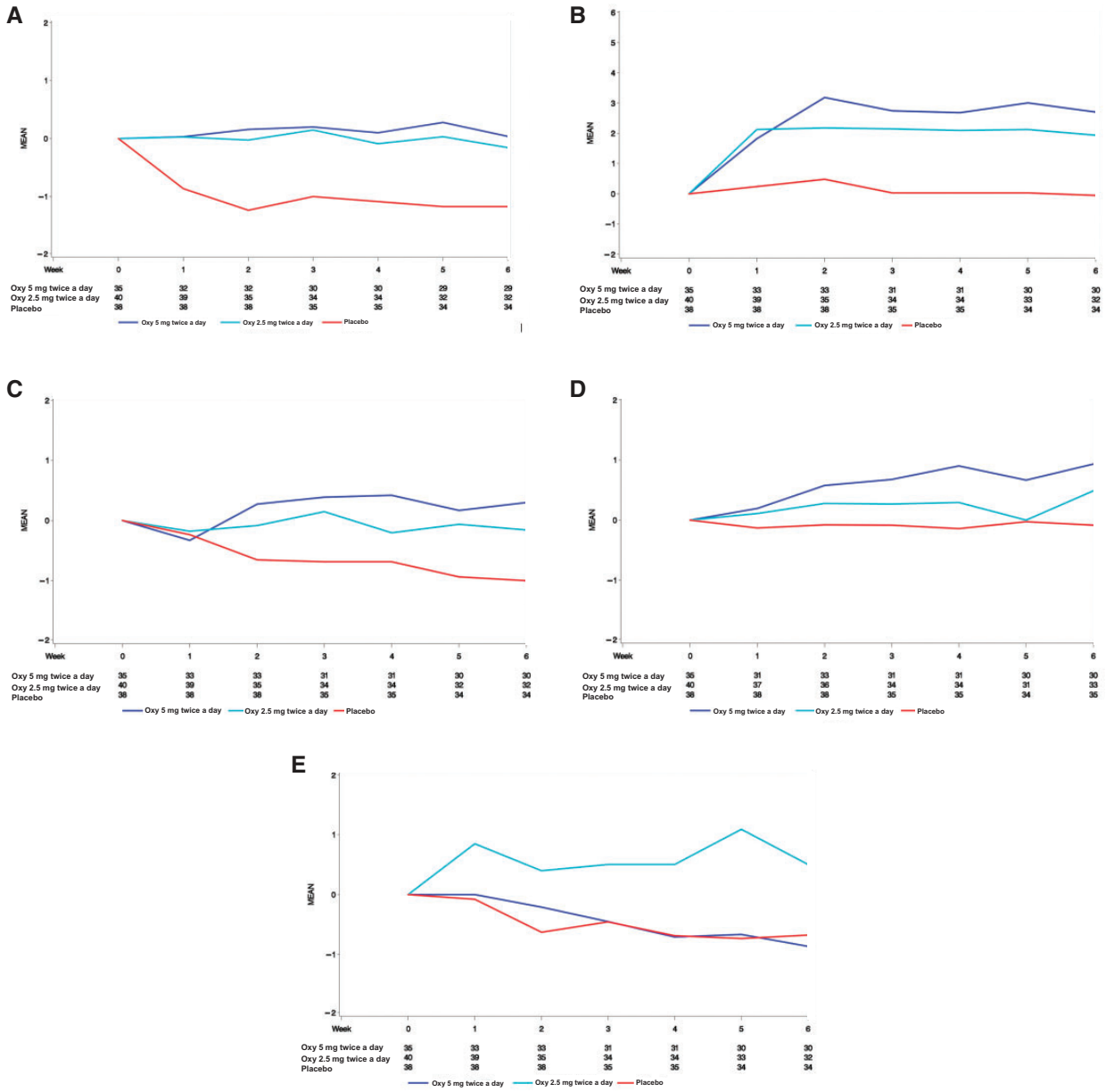

Figure 3. Mean change from baseline in select adverse events. Numbers under each week of treatment represent the number of evaluable patients at each week. Oxy = oxybutynin. **A)** Mean change from baseline in abdominal pain, **B)** Mean change from baseline in dry mouth, **C)** Mean change from baseline in constipation, **D)** Mean change from baseline in difficulty urinating, and **E)** Mean change from baseline in diarrhea.

mouth was the only symptom more frequent with oxybutynin than with placebo. Dry mouth was reported by study staff in 14 patients (33%) on Oxy5, 10 patients (21%) on Oxy2.5, and 3 patients (7%) on placebo (Oxy5 vs placebo $P = .004$, Oxy2.5 vs placebo $P = .06$). Diarrhea was reported less frequently with Oxy2.5 compared to placebo ($P = .049$), and there was no difference between Oxy5 and placebo (.173). Most of the other CTCAE 4.0 toxicities reported by study staff were grade 1, reported in fewer than 5% of patients, and not different from placebo. Grade 2 dry mouth was reported in five patients on oxybutynin 5 mg twice a day and one patient on 2.5 mg twice a day. In addition, grade 3 urinary tract pain was reported in one patient on oxybutynin 5 mg twice a day, and grade 3 headache was reported in one patient on 2.5 mg twice a day. Self-reported changes in baseline symptoms after the initiation of oxybutynin, which are probably a better measure of toxicity than are obtained with CTCAE criteria, are provided in Table 4 and Figure 3.

Among patients who started treatment, study discontinuation per treatment arm were as follows: 2 of 44 (5%) in the placebo arm, 5 of 46 (11%) in the Oxy2.5 arm, and 4 of 46 (9%) in the Oxy5 arm. There were no statistically significant differences in reasons for study discontinuation between the oxybutynin arms and placebo.

Discussion

The results from this study support the prestudy hypothesis that oxybutynin would improve HF frequency and severity. The

positive effect of treatment with oxybutynin on several HF interference measures and QoL supports that the magnitude of the effect was clinically meaningful. The degree of HF improvement with oxybutynin compares favorably with other agents that have been evaluated in prospective trials (8,9,18,27,41–43), with greater reduction in HF than has been observed with antidepressants and gabapentinoids, and similar to what has been reported with progesterone analogues.

The toxicity profile seen in the present trial contrasts with the toxicity profile seen in the study by Simon et al. (35), which used a higher dose (15 mg) of an extended-release formulation of oxybutynin. In that study, in addition to similar rates of dry mouth, patients on oxybutynin also reported more dyspepsia (12% vs 1%, $P = .009$) and diarrhea (10% vs 0%, $P = .006$) than did patients on placebo. Though some of the self-reported adverse effects (Table 4) were slightly worse on the Oxy2.5 arm compared with the Oxy5 arm, these differences are most likely due to random chance. The magnitude of the effect on HF on the trial by Simon et al. appears similar to what is reported in the present trial. As such, routine escalation of the dose beyond 10 mg daily may not be beneficial.

The treatment duration in this study was 6 weeks. As such, this trial demonstrated that oxybutynin provided short-term relief and that its short-term use was safe. By 6 weeks, HF score and frequency were reduced by 29% and 27%, respectively, with placebo, consistent with the placebo effect observed in other HF trials (8,9,18,27,41–43). HF trials have commonly been conducted for periods ranging between 4 and 12 weeks, without good scientific evidence that a particular study duration is superior. A joint analysis of five HF trials (44) and other HF trials lasting longer than 4 weeks (12,13,42) have consistently shown that the effect of evaluated drugs on HF plateaus at 4 weeks, suggesting that this is a reasonable period to assess short-term efficacy. Furthermore, there are no data to suggest that therapeutic efficacy on HF diminishes over time. However, long-term safety may be a different issue.

Anticholinergic drugs can be associated with acute mentation changes, delirium, electroencephalogram changes, and other negative cognitive effects (45–51). There are also reports linking anticholinergic drugs and dementia (52), although causality has not been established. The link with negative cognitive effects has been mostly reported in the elderly and in those with preexisting neurologic conditions. However, there are no good data to support or disprove that similar effects may occur in healthy younger women. The present trial did not conduct formal cognitive or psychometric testing. Patients in the Oxy2.5 arm did report slight worsening of episodes of confusion compared to placebo. It is also important to note that the population in this study was relatively young (mean [SD] = age 57 [8.2] years), and those taking other potent anticholinergic drugs were not allowed to participate. Patients and clinicians need to be aware of these concerns, particularly because cognitive impairment may be a problem among breast cancer survivors.

A possible advantage of oxybutynin for HF management over most antidepressants is the lack of interference with CYP2D6. This enzyme is important in the metabolic activation of tamoxifen, and it has been shown that concurrent use of CYP2D6 inhibitors leads to decreased plasma concentrations of endoxifen (the most potent tamoxifen metabolite). Whether this effect can affect the anticancer efficacy of this agent continues to be a matter of debate, with different studies showing mixed results (29,53–56). However, given this potential, patients and physicians may have concerns about using potent CYP2D6 inhibitors for HF treatment in women taking tamoxifen. Thus, oxybutynin may be an attractive choice for this patient population.

Although this study included only women, in a recent letter to the editor (57), Smith et al. reported a case of a male patient with severe and intrusive, drenching HF secondary to androgen-deprivation therapy for prostate cancer; these HFs were refractory to gabapentin and venlafaxine. The addition of oxybutynin 5 mg twice a day resulted in significant HF relief, a benefit that persisted after discontinuation of gabapentin and venlafaxine. After discontinuation of oxybutynin because of insomnia, dry mouth, and restless legs, HFs recurred but improved again within hours of restarting it, at a dose of 2.5 mg twice a day. Further prospective evaluation of oxybutynin in men with androgen deprivation–related HFs is planned.

Strengths of this study are the inclusion of breast cancer patients on active antiestrogen therapy, the use of standardized HF metric tools and questionnaires, and its prospective, randomized design. Limitations include the short duration, which precludes the demonstration of long-term safety (especially on cognition), and the missing data points in 15% of patients who started treatment. Despite these limitations, this study supports the short-term use of oxybutynin in patients with HFs refractory to other agents.

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Notes

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