Published in final edited form as:

J Support Oncol. 2011 ; 9(3): 105–112. doi:10.1016/j.suponc.2011.02.005.

A Phase III Randomized, Double Blind, Placebo-Controlled Study of Pilocarpine for Vaginal Dryness: NCCTG study N04CA¹

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Abstract

Purpose—Vaginal dryness is a common problem, for which effective and safe non-estrogenic treatments are needed. Based on preliminary promising data that pilocarpine attenuated vaginal dryness, the current trial was conducted.

Methods—A double-blind, placebo-controlled, randomized trial design was used to compare pilocarpine, at target doses of 5 mg twice daily and 5 mg four times daily, to a placebo. Vaginal dryness was recorded by patient-completed questionnaires at baseline and weekly for 6 weeks after study initiation. The primary endpoint for this study was the area under the curve (AUC) summary statistic comprised of the longitudinal responses obtained at baseline and through the six weeks of treatment to a numerical analogue scale asking patients to rate their perceived amount of vaginal dryness. The primary analysis was carried out by a single t-test using a two-sided

¹This study was conducted as a collaborative trial of the North Central Cancer Treatment Group and Mayo Clinic and was supported in part by Public Health Service grants CA-25224, CA-37404, CA-35195, CA-63848, CA-63849, CA-35431, CA-37417, CA-35113, CA-52352, CA-35103, CA-35119, CA-35267, CA-35269. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

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alternative to compare the collective pilocarpine treatment arms versus the collective placebo arms.

Results—A total of 201 patients enrolled in this trial. The primary analysis, comparing vaginal dryness symptoms in the collective pilocarpine arms against the placebo arm, did not reveal any benefit for the pilocarpine treatment. This finding was confirmed by other secondary analyses. Toxicity evaluation revealed more nausea, sweating, rigors, and urinary frequency with the pilocarpine arms compared to the placebo arm.

Conclusion—Pilocarpine did not alleviate vaginal dryness.

Background

Vaginal dryness is a major problem for many women after they become postmenopausal. In a study published in 2004(1), the incidence of vaginal or genital dryness and vaginal or genital irritation/itching was 27% and 19% respectively among postmenopausal women. Dennerstien et al(2) reported the incidence of post menopausal vaginal dryness around 25–47%. In two studies that looked at menopausal symptoms in breast cancer survivors, the reported incidence of vaginal dryness was higher (36–71%) (3,4) than that seen in the general postmenopausal public.

Vaginal dryness and irritation occur due to changes associated with estrogen depletion, which include a decrease in collagen and adipose content in the vulvar tissue, resulting in a decrease in the water retaining ability of the vagina (5). The prepuce of the clitoris atrophies more than the glans, which results in a loss of protection and increased risk of irritation and pain(5). Although systemic and/or local estrogen therapy is generally quite beneficial in relieving this problem, there are concerns with regards to giving estrogen to breast cancer survivors.

In patients with breast cancer, the causes of vaginal dryness can be multifactorial. Some patients may develop this problem solely related to their age and natural loss of estrogen. In addition, chemotherapy is known to cause ovarian failure in women(6). Patients with breast cancer who have experienced chemotherapy-induced ovarian failure have decreases in estradiol and increases in follicle-stimulating hormone, similar to those observed in postmenopausal women.(6)

In the early 1990s, the NCCTG Cancer Control Program addressed this clinical problem with a clinical protocol, which randomized women to receive a non-estrogenic vaginal lubricant (Replens) versus a placebo lubricating product. The results of this trial(7) provided information which suggested that vaginal dryness improved in patients receiving either product. Nonetheless, such products are cumbersome for many women and do not appear to work as well as estrogen.(8,9) Thus, better non-estrogenic treatments for vaginal dryness are desirable.

Pilocarpine is a cholinergic parasympathomimetic agonist that exerts a broad spectrum of pharmacologic effects, with predominant muscarinic activity (10,11). In appropriate doses, this drug can stimulate increased secretion by exocrine glands.

A phase III trial of pilocarpine in patients with Sjögren's syndrome has been reported, with the main outcome of this trial being related to oral and ocular dryness. Nonetheless, a statistically significant decrease in vaginal dryness was noted ($p=0.02$, 25% versus 14% reduction).(12) Pursuant to this, an abstract at the 2004 ASCO meeting reported on the utilization of pilocarpine (5 mg qid) for premenopausal women who had developed vaginal

dryness after receiving cyclophosphamide.(13) The authors reported that all four of these participants “experienced a marked clinical improvement” in vaginal dryness.

The above information suggested that oral pilocarpine may be able to treat vaginal dryness. The proposed mechanism of action is thought to be through cholinergic stimulation of the Bartholin’s glands, thereby providing increased mucus and moisture in the vaginal area. To better substantiate whether or not pilocarpine would be helpful for women suffering from vaginal dryness, the current randomized, double-blind, placebo-controlled, dose-finding clinical trial was developed.

Materials and Methods

Patients considered for this clinical trial were adult women clinically considered to be postmenopausal, or women with no childbearing potential. They either had a history of breast cancer (currently without evidence of active breast cancer) or did not want to take vaginal estrogen for a fear of an increased risk of breast cancer.

Patients must also have had significant vaginal complaints, defined as persistent vaginal dryness and/or itching of sufficient severity to make a patient desire therapeutic intervention. Symptoms were to have been present for at least 2 months prior to randomization.

A life expectancy of at least 6 months was required along with the ability to complete questionnaire(s) by themselves or with assistance. Patients could not have initiated or discontinued tamoxifen or aromatase inhibitors within 2 months prior to randomization or planned to initiate or discontinue these medications during the 6-week study. They could not have had evidence of an active vaginal infection or have been receiving concurrent chemotherapy. They were not allowed to have had acute iritis or have had a current or past history of using pilocarpine (regardless of purpose). There could be no planned use of any vaginal preparations during the study period (including any over the counter or herbal preparations) except lubricants used during sexual intercourse and no use of any vaginal preparations within 1 week of initiating study treatment other than lubricants used during sexual intercourse. Patients were not to have used any estrogen product within four weeks prior to randomization or planned to use such during the study period. Diagnoses of asthma, chronic obstructive pulmonary disease, coronary artery disease, narrow angle glaucoma, or known cholelithiasis were not permissible nor was hepatic or renal insufficiency, defined as a history of an elevation of aspartate aminotransferase ≥ 1.5 x the upper limit of normal (ULN) or creatinine ≥ 1.5 x ULN within the past year. Concurrent use of other anticholinergic medications, beta adrenergic antagonists or pharmacologic soy preparations was not allowed. Subjects could not have had a known history of a substantial cardiac arrhythmia, prior or concurrent pelvic radiation therapy, prior radical pelvic surgery, Bartholin gland surgery, vulvar or vaginal dysplasia, essential vulvodynia, vulvar vestibulitis, vaginal prolapse, Bartholin cyst/abscess, lichen sclerosis, lichen planus of the vulvovaginal region or desquamative vaginitis. Prior to study initiation, the patient must have had, within the prior 6 months, a history and physical examination, including a pelvic exam, with no history or suggestion of, vaginal infection.

Assessment of vaginal dryness is challenging and had been the subject of research available at the time this study was developed.(14) It has been measured by using vaginal pH strips to measure moisture,(15) maturation values, improvement in cytology, karyopyknotic index, and improvement in vaginal atrophy (>25% reduction in basal/para basal and intermediate cells).(16) Most vaginal dryness trials have measured participant and physician assessment (improvement in vaginal atrophy and freedom of symptoms).

None of these variables has a strong correlation with simple patient-reported perceived dryness.(16) Further, many of the other assessment methods are unnecessarily invasive and burdensome to the patient. We decided to use a simple numerical analogue as our primary endpoint as supported by a recent Cochrane review,(14) and used in a recent RTOG study of pilocarpine.(16)

Patients completed questionnaires at baseline and weekly for 6 weeks after study initiation. These questionnaires asked patients to rate vaginal dryness, vaginal itching, and vaginal discomfort during intercourse (if applicable) as being none, mild, moderate, severe, or very severe. The impact of vaginal dryness on activities of daily living was measured by asking subjects to rate, on a 0–10 point scale, how much vaginal dryness was bothersome for them in the past week, while similar questions were asked regarding how much vaginal dryness interfered with general activity, mood, normal work including both work outside the home and housework, relations with other people, sleep, and enjoyment of life. These questions were formatted in a manner similar to what has been utilized in multiple NCCTG cancer control studies.

In addition, potential symptoms that might be related to toxicities were addressed on the same 0–10 point scale with regards to nausea, vomiting, abnormal sweating, nervousness, interest in sexual relations, pain with intercourse, difficulty achieving an orgasm, trouble with blurred vision, chills, dizziness, or runny nose, and the need to urinate more frequently than usual. While the patients were on the study medications, they were also asked whether they had experienced any additional side effects that they related to the medication they were receiving.

Nurses called patients weekly to encourage questionnaire completion and to assess for any treatment related toxicities. Adverse events, reported using the CTCAE v. 3.0, specifically queried by the study nurses by weekly phone calls included nausea, rhinitis, rigors/chills, sweating, dizziness, and urinary frequency. Upon study completion, patients were asked to define whether they thought that the medication was 1) helpful with minimal side effects, versus 2) helpful but had too many side effects, versus 3) not helpful.

This study was reviewed as required by United States federal standards and all patients signed written consent forms. Patients were stratified by age (18–45 vs. 46–55 vs. 56–65 vs. >65 years), concurrent tamoxifen therapy (yes vs. no vs. unknown, e.g. on a blinded clinical study), concurrent aromatase inhibitor use (yes vs. no vs. unknown, e.g. on a blinded clinical study) and patient perception of vaginal symptom severity at baseline (mild vs. moderate vs. severe). They were then randomized, by the North Central Cancer Treatment Group randomization office, using a dynamic allocation procedure that balanced marginal distributions of the above stratification factors(17) to receive a target pilocarpine dose of 5 mg two times a day, or a target pilocarpine dose of 5 mg four times a day or identical appearing placebos (half with a target dose of two times a day while the other half with a target dose of four times a day). Pilocarpine was provided by Eisai Pharmaceuticals, Woodcliff Lake, New Jersey 07677. Placebos consisted of microcrystalline cellulose. Patients were titrated to their target dose (pilocarpine or placebo), by starting with 1 capsule (5 mg) daily and increasing it by 1 capsule every 3 days to their target dose (two times versus four times a day).

If the patient had any substantial toxicity (e.g., ≥grade 2 by NCI CTCAE, version 3.0) potentially ascribed to the study medication, the study drug was to be discontinued, but the patient was encouraged to continue to complete her study questionnaires.

Statistical methods

Placebo Comparison—This randomized, placebo-controlled study involved two placebo arms and two active treatment arms. Two placebo arms were employed to ensure blinding of the two active treatment arms which involved different dose levels. The first step in the analysis, hence, was to test whether there were differences in the results across the two placebo arms so that they could be combined into a single arm for subsequent analysis. This was carried out by running all of the analyses specified below to first compare the two placebo arms.

Primary Analysis—The primary endpoint was the area under the curve (AUC) summary statistic comprised of the longitudinal responses obtained at baseline and through the six weeks of treatment to a numerical analogue scale asking patients to rate their perceived amount of vaginal dryness, similar to what was used in the Vivino study(12). AUC summary statistics were chosen as they have been seen to be more stable and more sensitive to interpatient differences than other measures.(18) The primary analysis was carried out by a single t-test using a two-sided alternative to compare the collective pilocarpine treatment arms versus the collective placebo arms. Subsequent testing among the two pilocarpine dose levels was conducted. These multiple comparisons were done using a type I error rate of 2.5% to control the overall type I error rate.

Secondary Analyses—Multiple secondary analyses were undertaken to more fully describe the aspects of, and symptoms related to, vaginal dryness. The average scores of ordinal symptoms (listed in the methods section previously) at week 6 were evaluated using Wilcoxon tests, comparing the pilocarpine arms versus the collective placebo arms. The change in scores for each symptom, at the sixth week versus baseline, was calculated for each person. The averages of these changes from baseline scores were then compared via Wilcoxon tests. Similar to the primary analysis, in addition to the comparison of the combined arms, the two pilocarpine dose levels were compared by using Wilcoxon procedures. Repeated measures models were used as confirmatory analyses of the primary findings (data not shown). Toxicity data were evaluated across treatments arms by comparing the incidence rates, for each toxicity, among the treatment groups via Fisher's exact test.

Power considerations—The two-sample t-test for the primary analysis with 128 patients in the pilocarpine arms and 64 patients in the placebo arm had 80% power to detect a difference of 45% times the standard deviation.(19) This is considered a moderate effect size. The two-sample t-test for the secondary analysis to compare the two pilocarpine dose levels with 64 patients per group had an 80% power to detect a difference of 50% times the standard deviation and a 96% power to detect 66% times the standard deviation of the endpoint under study(19). These effect sizes have been classified as moderate and moderately small respectively with the former effect size (half a standard deviation) being declared the minimally clinically significant difference for various endpoints. Hence this study had sufficient power to detect all but clinically insignificant differences between the pilocarpine and placebo treatments, whether using the combined arms or individual treatment arms.

The impact of descriptive factors on the efficacy analysis was carried out comparing patient subgroups defined by whether patients had received previous adjuvant chemotherapy, previous hormonal therapy or a history of breast cancer (all yes versus no dichotomization). The results indicated that none of these descriptive factors had any impact on the efficacy results.

Missing data were accounted for in the analysis by sensitivity analysis using alternative imputation methods to assess the robustness of the results.(20)

Results

Baseline characteristics

This study accrued subjects between 12/15/06, and 5/1/09, with a total of 201 patients enrolled from 22 NCCTG member sites. Baseline patient characteristics were similar in the three treatment groups, as are detailed in Table 1. A consort diagram (Figure 1) illustrates patient study flow.

Placebo arm combination

The primary efficacy analysis (AUC) indicated that there was no difference between the two placebo dose levels (mean (sd): 63.2 (24.2) vs. 64.1 (24.3), $p=0.81$). Similarly there were no differences among the ten vaginal dryness secondary endpoints listed in the methods section, across the two placebo dose levels. Hence, for the remainder of the analysis, the two placebo arms were combined into a single arm for comparison with the pilocarpine treatments.

Vaginal dryness efficacy

The primary analysis, comparing vaginal dryness symptoms in each of the pilocarpine arms against the combined placebo arm, did not reveal any benefit for either of the pilocarpine treatment arms, illustrated in figure 2. The mean score improved from 39/100 to 65/100 for pilocarpine 2 times/day arm, 43/100 to 79/100 for pilocarpine 4 times/day arm, and 44/100 to 73/100 for placebo arm. None of the other questionnaire-determined inquiries, defined in the methods section, were statistically significantly improved with either of the pilocarpine arms compared to the combined placebo arm. Further data supporting a lack of benefit is derived from a question that the patients completed at the end of the study, which inquired about whether the patient felt that the study medication was beneficial. Data depicted in table 2 illustrate that patients did not find pilocarpine to be any better than the placebo.

Toxicity

Toxicity differences between study arms are illustrated in Table 3, which revealed that there was more trouble with nausea, sweating, rigors, and urinary frequency with the pilocarpine arms, compared to the placebo arm. Toxicity information from the symptom experience diary (detailed in the methods section) did not note any other toxicities in either of the pilocarpine arms, compared to the placebo arm, with the exception of a decreased interest in sexual relations in the higher dose pilocarpine arm. However, the last toxicity question asked patients if they had other toxicities that they related to the study medication, revealing that there was a higher incidence of various other toxicities in the pilocarpine arms (table 4). In addition, further supporting that there was more toxicity with pilocarpine is illustrated in table 5, which outlines the reasons why patients discontinued the study; showing that subjects receiving pilocarpine were more likely to discontinue study participation due to toxicity.

Discussion

The results of this clinical trial did not support the pre-study hypothesis. There was no suggestion that pilocarpine was beneficial in decreasing vaginal dryness in the study population. In addition to not causing any evidence of benefit, the pilocarpine was associated with some toxicity. The toxicities that were seen in this trial (nausea, sweating, rigors, and urinary frequency), are congruent with the most common side effects from pilocarpine, seen at the doses up to 10 mg TID, in other studies; these include sweating (29–

68%), nausea (6–15%), rhinitis (5–14%), diarrhea (4–7%), chills (3–15%), flushing (8–13%), urinary frequency (9–12%) and asthenia (6–12%)(21)

Thus, pilocarpine can not be recommended for use for treatment of vaginal dryness, despite the preliminary pilot information that suggested that it might have been beneficial.

Alternative non-estrogenic means are necessary for treating vaginal dryness. Along this line, new information supports that DHEA (dehydroepiandrosterone) was able to decrease vaginal dryness, without evidence of it increasing systemic estrogen and/or testosterone concentrations (22–25). Further information with regard to the utility of this therapy in breast cancer survivors would be of value.

Acknowledgments

Funding for this clinical trial was provided by the National Cancer Institute. Pilocarpine and placebos were provided by Eisai Pharmaceuticals, Woodcliff Lake, New Jersey, 07677.

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*AUC analysis can accommodate the missing data points between week 1 and week 6

Figure 1.
Patient Consort Diagram

NCCTG

Figure 2.
Changes from baseline in vaginal dryness scores over study weeks by study arm

Table 1

On-study patient characteristics

	Collective Placebo (N=64)	Pilocarpine 2 times/day (N=65)	Pilocarpine 4 times/day (N=66)	Total (N=195)
Age				
Mean (SD)	54.6 (7.93)	55.1 (8.14)	54.7 (7.25)	54.8 (7.74)
Range	34.0–75.0	36.0–74.0	41.0–74.0	34.0–75.0
Race				
White	60 (94%)	63 (97%)	65 (99%)	188 (96%)
Black or African American	3 (5%)	1 (2%)	0 (0%)	4 (2%)
American Indian or Alaska Native	1 (1.6%)	0 (0%)	1 (2%)	2 (1%)
Unknown: Patient unsure	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Tamoxifen				
Yes	10 (16%)	10 (15%)	9 (14%)	29 (15%)
No	54 (84%)	54 (83%)	56 (85%)	164 (84%)
Unknown	0 (0%)	1 (2%)	1 (2%)	2 (1%)
Current Aromatase Inhibitor				
Yes	36 (56%)	37 (57%)	38 (58%)	111 (57%)
No	28 (44%)	27 (42%)	27 (41%)	82 (42%)
Unknown	0 (0%)	1 (2%)	1 (2%)	2 (1%)
Severity of Vaginal Symptoms				
Mild	6 (9%)	6 (9%)	6 (9%)	18 (9%)
Moderate	30 (47%)	30 (46%)	30 (46%)	90 (46%)
Severe	28 (44%)	29 (45%)	30 (46%)	87 (45%)
Breast Cancer History				
Yes	55 (86%)	59 (91%)	58 (88%)	172 (88%)
No	9 (14%)	6 (9%)	8 (12%)	23 (12%)

Table 2

Patient assessment of study medication benefit at the end of the study

	Collective Placebo (N=64)	Pilocarpine 2 times/day (N=65)	Pilocarpine 4 times/day (N=66)	Total (N=195)	p value
Do you think the study medication you took was helpful?					0.132
Missing	14	11	17	42	
Yes, with minimal side effects	25 (50%)	23 (42.6%)	22 (44.9%)	70 (45.8%)	
Yes, but too many side effects	2 (4%)	4 (7.4%)	9 (18.4%)	15 (9.8%)	
No, was not helpful	23 (46%)	27 (50%)	18 (36.7%)	68 (44.4%)	

Table 3

CTCAE-Detected Toxicities

	Collective Placebo (N=63)		Pilocarpine 2 times/day (N=65)		Pilocarpine 4 times/day (N=66)		Kruskal- Wallis p- value
		%		%		%	
RIGORS							0.002
0-None	61	97%	51	78%	49	74%	
1-Mild	2	3%	14	22%	16	24%	
2-Moderate	0	0%	0	0%	1	2%	
URINARY FREQUENCY							0.006
0-None	51	81%	44	68%	37	56%	
1-Mild	12	19%	20	31%	24	36%	
2-Moderate	0	0%	1	2%	5	8%	
NAUSEA							0.030
0-None	56	89%	49	75%	46	70%	
1-Mild	6	10%	13	20%	18	27%	
2-Moderate	1	2%	3	5%	2	3%	
SWEATING							0.062
0-None	44	70%	36	55%	33	50%	
1-Mild	14	22%	19	29%	23	35%	
2-Moderate	5	8%	10	15%	10	15%	

Table 4

Incidence of other toxic symptoms related to the study medication

Week	Collective Placebo (N=64)	Pilocarpine 2 times/day (N=65)	Pilocarpine 4 times/day (N=66)	P-value
1	17/61 (28%)	27/62 (44%)	25/54 (46%)	0.085
2	17/59 (29%)	21/55 (38%)	26/52 (50%)	0.073
3	14/59 (24%)	18/55 (33%)	28/53 (53%)	0.005
4	13/54 (24%)	13/54 (24%)	25/52 (48%)	0.010
5	14/57 (25%)	13/56 (23%)	22/48 (46%)	0.022
6	11/59 (19%)	11/54 (20%)	20/51 (39%)	0.027

Table 5

Reasons for study discontinuation

Reason End Treatment	Collective Placebo (N=64)	Pilocarpine 2 times/day (N=65)	Pilocarpine 4 times/day (N=66)	Total (N=195)	P value
Missing	1	0	0	1	0.045 /
Completed Study Per Protocol	59 (94%)	51 (79%)	49 (74%)	159 (82%)	
Refused Further Treatment	1 (2%)	2 (3%)	6 (9%)	9 (5%)	
Adverse Event	2 (3%)	10 (15%)	7 (11%)	19 (10%)	
Other	1 (2%)	2 (3%)	4 (6%)	7 (4%)	

/ Chi-Square