Nonhormonal therapy for endometriosis: a randomized, placebo-controlled, pilot study of cabergoline versus norethindrone acetate

Amy D. DiVasta, M.D., M.M.Sc.,[a,b,c] Catherine Stamoulis, Ph.D.,[a,c] Jenny Sadler Gallagher, M.P.H.,[a,b] Marc R. Laufer, M.D.,[b,c,d,e] Raymond Anchan, M.D., Ph.D.,[b,c,e] and Mark D. Hornstein, M.D.[b,c,e]

[a] Division of Adolescent Medicine, Boston Children's Hospital, [b] Boston Center for Endometriosis, [c] Harvard Medical School, [d] Division of Gynecology, Department of Surgery, Boston Children's Hospital, and [e] Division of Fertility and Reproductive Surgery, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Massachusetts

Objective: To estimate the efficacy and safety of a novel nonhormonal therapeutic agent, cabergoline, compared with that of the standard clinical therapy, norethindrone acetate (NETA), for the treatment of endometriosis-associated pain in young women with endometriosis.
Design: Randomized, double-blind, placebo-controlled pilot study.
Setting: Tertiary care center.
Patient(s): Women (n = 9) with surgically confirmed endometriosis.
Intervention(s): A random, double-blind assignment to either NETA (5 mg/day) + placebo twice weekly or cabergoline (0.5 mg) twice weekly + placebo daily for 6 months.
Main Outcome Measure(s): We collected the measures of pelvic pain and laboratory parameters every 3 months.
Result(s): We observed a decrease in pain scores and increase in pain relief in women randomized to receive cabergoline, who appeared to show similar or more improvements than women treated with NETA. The serum measures of vascular endothelial growth factor receptor 1 declined over 6 months in those who received cabergoline. Cabergoline was well tolerated, and no serious adverse events occurred.
Conclusion(s): Safe, effective adjunct treatments are lacking for patients with endometriosis who do not respond to standard care. Because the growth of endometriosis requires angiogenesis, blood vessel growth is an attractive therapeutic target. This pilot study suggests that cabergoline, a vascular endothelial growth factor pathway inhibitor, is an effective therapeutic option for women with chronic pain due to endometriosis. Building upon this investigation, we will conduct larger, randomized trials of cabergoline, advancing research on the best treatments for endometriosis—particularly disease resistant to hormonal therapies.
Clinical Trial Registration Number: clinicaltrials.gov; registration number NCT02542410. (Fertil Steril Rep® 2021;2:454–61. ©2021 by American Society for Reproductive Medicine.)

Received February 17, 2021; revised and accepted July 19, 2021.
A.D.V. reports grants from Marriott Daughter's Foundation, during the conduct of the study, and grants from Merck Pharmaceuticals Investigator-Initiated Research Award, outside the submitted work. C.S. has nothing to disclose. J.S.G. reports grant from Richard E. and Nancy P. Marriot Foundation. M.R.L. reports grants from J Willard & Alice S Marriott Foundation and Marriott Daughter's Foundation; royalties from Wolters Kluwer; consulting for NextGen Jane; and a leadership or fiduciary role in Boston Center for Endometriosis and Center for Young Women's Health. R.A. has nothing to disclose. M.D.H. reports royalties from UpToDate.
Study financial support was provided by the Marriott Daughters' Foundation. No sponsor or donor had any role in the development, conduct, analysis, or presentation of the study or its findings. We wish to acknowledge the excellent care of the Experimental Therapeutics Unit nurses as well as our patients and their families, who made this research possible.
Reprint requests: Amy D. DiVasta, M.D., M.M.Sc., Division of Adolescent Medicine, Boston Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02048 (E-mail: amy.divasta@childrens.harvard.edu).

Fertil Steril Rep® Vol. 2, No. 4, December 2021 2666-3341

https://doi.org/10.1016/j.xfre.2021.07.003

Key Words: Angiogenesis, cabergoline, endometriosis, norethindrone acetate, nonhormonal therapy

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/xfre-d-21-00022

Endometriosis is a chronic illness that begins during adolescence and young adulthood (1, 2). It affects ~49% of adolescents with chronic pelvic pain and 10% of all women of reproductive age (3, 4). Endometriosis has multiple clinical manifestations, including dysmenorrhea, acyclic pelvic pain, nausea, dyspareunia, dyschezia, fatigue, and infertility (1). Women must cope with reduced productivity, missed academic and work opportunities, and social consequences (5). Endometriosis is a chronic disease that progresses significantly over time in ~50% of patients (6, 7). Appropriate management involves not only the prompt initiation of therapy but also the maintenance of therapy for a protracted length of time.

Endometriosis-associated pelvic pain can be treated medically and surgically. Medical treatments have centered on hormonal manipulation to either induce a hypoestrogenic milieu or antagonize estrogen action; the treatments commonly include combined oral contraceptives, progestins, or gonadotropin-releasing hormone agonists (8, 9). These therapies are often limited by the lack of success, high cost, or side effects (9, 10). Hormonal treatments do not cure endometriosis; after medication discontinuation, pain scores often rise back to baseline values (11–13). Approximately 50% of women with endometriosis experience recurrent symptoms over a 5-year period, irrespective of the treatment approach (1, 14). Because there is no cure, there exists a pressing need to evaluate novel, nonhormonal treatments to ameliorate the chronic course of the disease and prevent the ongoing suffering for these women.

Although hormonal therapy has been the mainstay of treatment, novel targets for treatment may be found among causative pathways of the disease. The development of endometriosis involves interactions between hormonal, immunologic, inflammatory, and proangiogenic processes (1). Theories hold that endometriotic cells reach the peritoneal cavity via retrograde menstruation, coelomic metaplasia, and lymphatic or vascular metastasis. In order for these cells to get implanted and subsequently develop into endometriosis lesions, these cells must establish new, adequate blood supply for their formation and maintenance (15). Angiogenesis and concomitant neurogenesis play a key role in the ectopic implantation of endometrial tissue, its development into endometriosis, and the development of chronic pain (16, 17). Angiogenic pathways are stimulated by inflammatory cells (macrophages, lymphocytes, and mast cells) and the many angiogenic factors they produce, including vascular endothelial growth factor (VEGF) and tumor necrosis factor alpha (TNF-α) (18). Several antiangiogenic agents that target the angiogenesis pathway have been successfully used in animal models of endometriosis (19). However, these investigative agents can induce severe side effects, including hypertension, hypothyroidism, diarrhea, bleeding events, and hemorrhage, and are teratogens, precluding their use in young and otherwise healthy women (20, 21).

Dopamine receptor 2 (DRD2) agonists are a theoretical alternative to commercial antiangiogenic agents. In animal models, DRD2 agonists inhibit pathologic angiogenesis in tumors by inactivating VEGF receptor 2 (VEGF-R2) signaling (22, 23). In contrast to other antiangiogenic agents, this type of medication has an acceptable safety profile and does not interfere with the normal establishment and progression of pregnancy (24–26). Cabergoline and quinagolide, both DRD2 agonists, inhibited angiogenesis in a mouse model of angiogenesis (27). In a preliminary study of 9 women with endometriosis and hyperprolactinemia, quinagolide induced a 69.5% reduction in the size of endometriosis lesions over 20 weeks (28). However, the investigators did not collect data regarding pain or bleeding outcomes.

Thus, our objective was to explore the effect of experimental therapy, cabergoline, versus the effect of the standard therapy, norethindrone acetate (NETA), for the treatment of pelvic pain due to endometriosis. We hypothesized that cabergoline would inhibit endometriosis-mediated neuroangiogenesis and that after 6 months, subjects randomized to receive cabergoline would demonstrate decreased pain measures, improved functional disability scores, and decreased circulating angiogenic and inflammatory biomarkers compared with subjects randomized to receive NETA.

MATERIALS AND METHODS

Study Design

The study was a randomized, double-blind, placebo-controlled, 6-month pilot study conducted at Boston Children's Hospital and Brigham and Women's Hospital from 2016 to 2018. We screened 74 women for study eligibility (Supplemental Fig. 1, available online). Eligible women were aged 15–40 years, were premenopausal, and had surgically confirmed endometriosis, determined using laparoscopy within 2 years prior to study baseline. The participants were experiencing pelvic pain over the last month, as determined using a visual analog scale (VAS) score of ≥ 3, where 0 indicates the absence of pain and 10 corresponds to unbearable pain. Participants were excluded if they were using other hormonal medications (such as combined oral contraceptive pills), thrombotic disease, or had contraindications to the study medications (impaired liver function, breast cancer, cardiac valvular disorders, etc.).

Patients

Of 73 subjects who were initially approached regarding the study, 39 were lost to follow-up, 17 were not interested, 8 were ineligible, and 9 were consented, enrolled, and

randomized into 2 groups (Supplemental Fig. 1). Group 1 received 5 mg of oral NETA (Aygestin; Amneal Pharmaceuticals, Bridgewater, NJ) daily + placebo tablet twice weekly. Group 2 received oral 0.5 mg of cabergoline (Teva Pharmaceuticals, North Wales, PA) twice weekly + placebo tablet daily (Food and Drug Administration Investigational New Drug application 132882).

All the medications were dispensed by the research pharmacy in a gelatin capsule and were identical in appearance. The principal investigator, study staff, and participants remained blinded to the treatment assignment throughout the 6-month study. The Boston Children's Hospital and Brigham and Women's Hospital institutional review boards approved the protocol. Written informed consent was obtained from all the participants (clinicaltrials.gov NCT02542410).

Study Assessments

The participants presented for in-person research visits at baseline (pretreatment), 3 months, and 6 months. Additional telehealth assessments were conducted at 6 and 18 weeks. Medication compliance was assessed using pill counts and participant-completed pill logs at each visit. The participants also reported the mean number of non-narcotic pain tablets taken per week.

The primary endpoint was the measurement of pain in multiple dimensions, including 4 core chronic pain outcome domains (physical functioning, pain intensity, emotional functioning, and feeling of improvement), as recommended by an expert consensus-based statement (29). The measurements occurred at each in-person study visit. The Brief Pain Inventory (BPI) interference scale was the primary outcome variable (30, 31). The BPI is a 7-item, self-reported measure designed to assess the extent to which pain interferes with various components of functioning, including physical and emotional functioning and sleep (32). The VAS was used to rate pain intensity (0–10 numerical rating scale). The VAS scores were categorized as none or mild (0–3), moderate (4–6), and severe (7–10) pain. Emotional functioning was measured using the Beck Depression Inventory-II, with scores categorized as follows: $<$10, minimal or no depression; 10–18, mild to moderate; 19–29, moderate to severe; and 30–63, severe depression (33). Participant ratings of overall improvement were assessed using the patient global impression of change scale, a 7-point rating scale asking the following question: "Since beginning this study, how would you describe the change (if any) in activity limitations, symptoms, emotions, and overall quality of life?" The scores were categorized as follows: 1–3, no or minimal change; 4–5, moderate improvement; and 6–7, definite or considerable improvement (34, 35). The Functional Disability Inventory scale was used to measure the impact of physical health on the performance of regular daily activities; the scores ranged from 0 to 60, with a higher score indicating more impairment (36).

Serum samples were obtained for the measurement of inflammation and the assessment of the angiogenic pathway. The markers included VEGF, TNF-α, placental growth factor, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, VEGF receptor 1 (VEGF-R1), monocyte chemotactic protein-1, interleukin 8 (IL-8), E-selectin, and IL-1β, based on the results of previous studies (37–42). Urine samples were obtained at each visit to allow for the performance of a pregnancy test and for the assessment of a urinary marker of oxidative stress [8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG)]. The samples were assayed at the Clinical and Epidemiology Research Laboratory, Department of Laboratory Medicine, Boston Children's Hospital.

Height was measured in a standardized fashion using the same wall-mounted stadiometer. Weight was measured on the same digital scale, with patients clothed in a hospital gown after voiding. Body mass index was calculated as weight (kg)/(height [m])^2. Pulse and blood pressure (vital orthostatic signs) were measured in both supine and standing (after 3 minutes of standing to reach equilibrium) positions. At each study visit, each participant was given an investigator-developed standardized symptom questionnaire that asked about common hormonal symptoms, including fatigue, mood changes, breast tenderness, and nausea. The participants were asked to self-report the presence or absence of each symptom. If they had a positive response, they were asked to rate the frequency and severity of their symptom. Adverse effects experienced during the treatment, such as uterine bleeding, were also recorded and quantified. We used the common terminology criteria for adverse events (CTCAE, v5.8) for standardized grading of adverse events. To assess patient safety, we also measured serum hemoglobin A1c levels, erythrocyte sedimentation rate, and serum creatinine levels as well as performed lipid panels and liver function tests (aspartate transaminase, alanine aminotransferase, total bilirubin).

Statistical Analyses

Sample size. Given its design as a pilot study, the sample size was chosen to provide estimates for the change over time in each group while minimizing the number of subjects exposed to the study treatments. Assuming an 80% trial completion rate, we recruited 5 patients to each arm to have at least 4 completers in each randomization group.

The change in pain score over time, measured using the BPI, was the primary outcome of interest. Given the small sample size, no statistical test or model would have had sufficient power to estimate significant differences. Therefore, only trends were reported. The summary statistics (median and interquartile ranges) of pain scores and other secondary outcomes were presented.

RESULTS

Patients

Of the 9 women who completed the baseline measurements, 1 participant from each group dropped out before the 6-week study visit, leaving 3 in the NETA group and 4 in the cabergoline group who completed the 6-month study. The subjects were adult women (median age 24.8 years, range 21.8–41.0 years) with a median body mass index of 27.9 kg/m^2. Approximately half of the subjects self-identified as White; 1 subject

TABLE 1

Demographic characteristics and baseline measurements of 9 women with endometriosis, in total and separated based on treatment group.

Characteristic	All participants N = 9	NETA n = 4	Cabergoline n = 5
Age, y [median (IQR)]	24.8 (4.5)	25.3 (11.5)	24.9 (3.5)
BMI, kg/m^2 [median (IQR)]	27.9 (10.2)	27.5 (0.9)	37.1 (23.3)
Race (n; %)			
White	5 (55.6)	2 (50)	3 (60)
Black/African American	3 (33.3)	2 (50)	1 (20)
Asian	0	0	0
Other	1 (11.1)	0	1 (20)
Ethnicity (n; %)			
Hispanic	1 (11.1)	0	1 (20)
Occupation (n; %)			
Student	2 (22.2)	1 (35)	1 (20)
Employed (part-time or full-time)	6 (66.7)	3 (75)	3 (60)
Tobacco user (%)	0	0	0
Alcohol user (%)	7 (77.8)	4 (100)	3 (60)
Baseline pain medications (n;%), tablets/wk			
Narcotic	1 (11.1); 29	0	1 (20); 29
Prescription (non-narcotic)	1 (11.1); 14	0	1 (20); 14
Over the counter (including herbal)	6 (66.7)	4 (100)	2 (40)

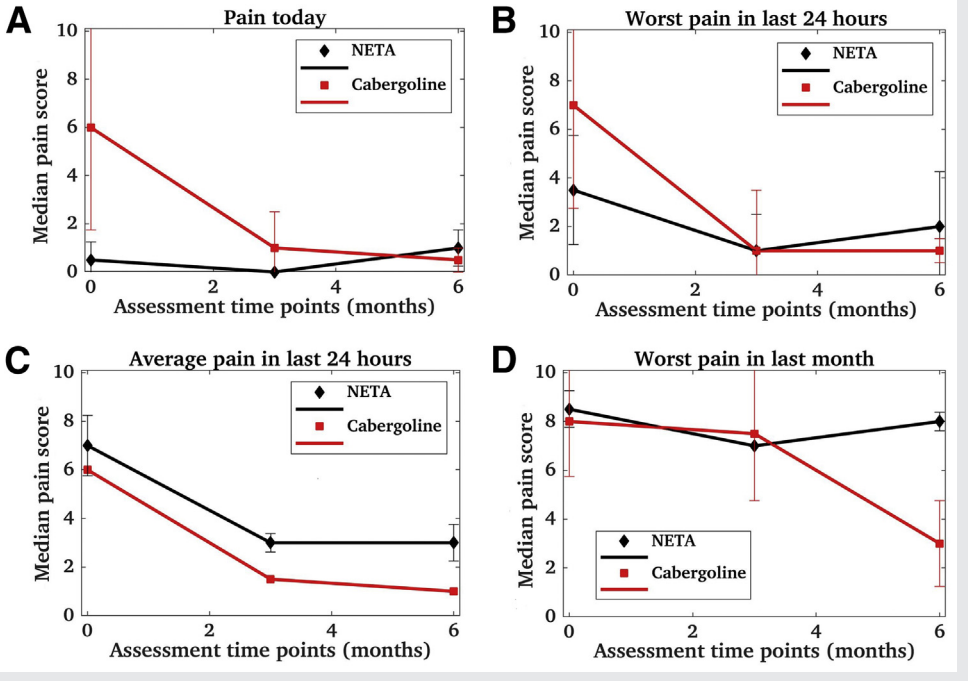
BMI = body mass index; IQR = interquartile range; NETA = norethindrone acetate.

DiVasta. Novel treatment for endometriosis. Fertil Steril Rep 2021.

identified as Hispanic. The groups did not differ in their baseline demographic characteristics (Table 1). All the subjects had American Society for Reproductive Medicine stage 1 or 2 endometriosis at the time of laparoscopy.

One subject receiving NETA and 1 subject receiving cabergoline discontinued participation before the 6-week phone call (Supplemental Fig. 1). The reasons for discontinuation were fatigue and increased pain for the one receiving NETA

FIGURE 1



Changes in the measurement of pain over 6 months in 9 women randomized to receive either cabergoline or NETA. (A) Pain severity score today. (B) Worst pain severity score in the last 24 hours. (C) Average pain severity score. (D) Worst pain severity score in the last month. NETA = norethindrone acetate.

DiVasta. Novel treatment for endometriosis. Fertil Steril Rep 2021.

and fatigue, hot flashes, mood swings, and bladder incontinence for the one receiving cabergoline. Based on the pill counts, 4 (57%) of 7 subjects missed at least 1 dose of the study medications before the 3-month visit; this number increased to 86% at 6 months. The reported compliance did not vary between the trial arms. Seven participants completed the 6-month trial.

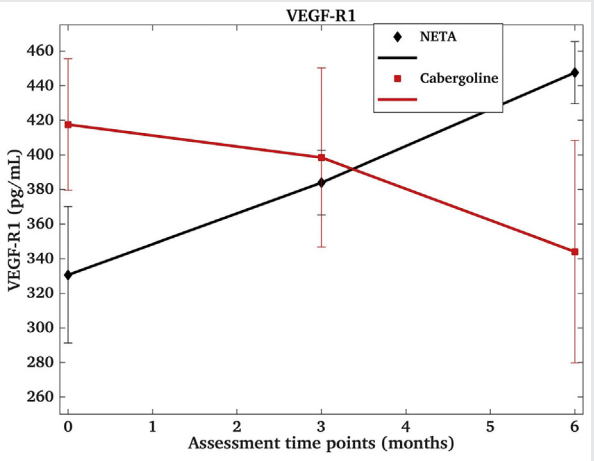
Symptom Changes and Quality of Life Assessment

Upon the assessment of pain at the baseline (range 0–10), the subjects in the cabergoline group reported a greater severity of current pain (6.0 vs. 0.5) and worst pain in the last 24 hours (7.0 vs. 3.5) than those in the NETA group (Supplemental Table 1, available online). They also reported less relief of pain (from the pain treatments or medications provided, range 0%–100%) than those in the NETA group (20% vs. 85%, respectively, Supplemental Table 1). The average pain and best or least pain were not different between the groups. Neither group reported much interference with general activity, walking ability, working, or sleeping due to pain.

Figure 1 shows how pain measurements (using both the VAS and BPI) changed over time. Over 6 months of the treatment, subjects receiving cabergoline demonstrated improvements in their worst pain severity (Fig. 1B and D), both in the last 24 hours (from 7.0 to 1.0) and in the last month (from 8.0 to 3.0). Improvements over time were also seen in current pain severity (Fig. 1A), least pain severity, the percentage of pain relief achieved (Supplemental Table 1), and average pain severity (Fig. 1C). The subjects receiving NETA had a similar trend in their improvements in average pain, although more substantial changes were seen in the cabergoline group at 6 months (Fig. 1C). Little change in other measures occurred in those receiving NETA (Supplemental Table 1). The mean 6-month decrease in pain intensity (worst pain in the last 24 hours) was 86% in the cabergoline group and 43% in the NETA group. Similarly, average pain decreased by 83% in the cabergoline group and 57% in the NETA group. At the beginning of the study, 1 of 4 women in the NETA group and 1 of 5 women in the cabergoline group used various non-narcotic analgesics for endometriosis-associated pain (Table 1). At the 6-month follow-up visit, the percentage of analgesic users did not change, but the number of non-narcotic analgesic tablets used per week increased in the NETA group (Supplemental Table 1).

Neither group showed a clinically meaningful amount of depressive symptoms (measured using the Beck Depression Inventory-II) at any time point. The subjects also did not report much physical trouble or difficulty doing activities of daily living, as determined using the Functional Disability Inventory scale (Supplemental Table 1). The participants' impression of change due to the study treatment was measured using the patient global impression of change scale. At 3 months, 33% of the subjects in the NETA group reported a moderate or high degree of change compared with 25% of the subjects in the cabergoline group. At 6 months, the proportion reporting a moderate or high degree of change increased to 66% in the NETA group and 50% in the cabergoline group.

FIGURE 2



Changes in the measurement of VEGF-R1 over 6 months in 9 women randomized to receive either cabergoline or NETA. NETA = norethindrone acetate; VEGF-R1 = vascular endothelial growth factor receptor 1.

DiVasta. Novel treatment for endometriosis. Fertil Steril Rep 2021.

Biomarkers

During the 6-month pilot study, the serum VEGF-R1 levels declined in the subjects receiving cabergoline (from 417.6 pg/mL to 344.1 pg/mL), whereas these increased in those receiving NETA (from 330.7 pg/mL to 447.6 pg/mL, Fig. 2). Both the groups showed small declines in the serum VEGF concentrations. The levels of most serum inflammatory biomarkers did not change (Supplemental Table 1). The levels of IL-8 decreased by almost 50% in those receiving cabergoline (from 9.5 pg/mL to 4.5 pg/mL) but started low and did not changing over time in those receiving NETA (from 4.8 pg/mL to 4.9 pg/mL).

Safety Profile Measurement

No subject developed orthostatic changes in blood pressure or pulse during study participation. The median alanine aminotransferase and aspartate transaminase levels were similar between the groups at the time of trial initiation and remained within the normal laboratory range throughout. Neither treatment regimen led to deleterious changes in lipid profiles.

Information regarding side effects was solicited using an investigator-developed symptom questionnaire. All reported side effects were rated by the participants as mild or moderate, except for 3 instances, which were rated as severe. One participant (NETA group) reported severe headache. One participant in each treatment group reported severe abdominal pain or bloating. These symptom changes that occurred following the initiation of study medications are listed in Table 2. Of the 40 symptom changes reported in the symptom questionnaire, 20 (50%) were rated by the participants as mild, 17 (43%) as moderate, and 3 (7%) as severe. The most common changes reported were abdominal cramps or bloating, feeling tired, and weight gain. For the 7 subjects who completed the

TABLE 2

Patient-reported side effects during the 6-month pilot study following study medication initiation.[a]

Adverse event	NETA n = 4	Cabergoline n = 5
	n (number of participants reporting)	
Mood changes	1	1
Upset stomach or nausea	0	4
Feeling tired or weak	3	2
Headache	1	1
Breast tenderness	1	1
Constipation	1	3
Dizziness	0	0
Hot flashes	1	2
Numbness or tingling	1	2
Abdominal cramps or bloating	2	3
Trouble sleeping	0	2
Hair growth	0	2
Acne	1	1
Weight gain	2	2
Changes in uterine bleeding		
Heavier flow	1	2
Lighter flow	0	0
Amenorrhea	0	0
Irregular or spotting	1	3

NETA = norethindrone acetate.

[a] The side effects were solicited using an investigator-developed symptom questionnaire. All reported side effects, except 3, were rated as mild or moderate. One participant (NETA) reported severe headache. One participant in each treatment group reported severe abdominal bloating.

DiVasta. Novel treatment for endometriosis. Fertil Steril Rep 2021.

trial, the average weight change was >1.8 kg over 6 months (>1.3 kg for the cabergoline group vs. >2.5 kg for the NETA group). The investigators identified only 2 CTCAE grade 2 adverse events: 1 participant with fatigue that interfered with the activities of daily life, which was not relieved by rest, and 1 participant with abdominal bloating and pain that limited her daily activities or work.

DISCUSSION

In this randomized pilot study, we demonstrated the tolerability of a novel, nonhormonal medication—cabergoline—for the treatment of chronic pelvic pain due to endometriosis. Over 6 months, we observed a decrease in the pain scores and increase in pain relief in women randomized to receive cabergoline, who appeared to show similar or more improvements than women treated with NETA.

It is well established that angiogenesis is involved in the pathophysiology of endometriosis (43). The level of VEGF is higher in the peritoneal fluid of patients with endometriosis than in that of controls and higher in the peritoneal fluid of patients with more severe disease than in that of women with less severe disease (44–50). Oxidative stress, endothelial dysfunction, and inflammatory response due to the production of prostaglandins, chemokines, and cytokines have also been implicated in the pathogenesis of endometriosis (4, 51–53). The peritoneal fluid of patients with endometriosis contains factors, including IL-8 and TNF, that induce neutrophil VEGF release (54).

Based on previous research, we believed that the use of an antiangiogenic agent would improve symptoms for women with endometriosis (27, 28). However, majority of these investigative agents can induce severe side effects and are teratogens, precluding their use in young, otherwise healthy women (20, 21). We hypothesized that DRD2 agonists would be potential alternatives to commercial antiangiogenic agents because of their acceptable safety profile and lack of interference with the menstrual cycle or the normal establishment and progression of pregnancy (24–26). Dopamine receptor 2 agonists, such as cabergoline, inhibit the growth of human endometrial tissue xenografts in mice and reduce VEGF-R2 phosphorylation (27, 55). These animal study results led to a pilot study for the evaluation of DRD2 agonists in the treatment of peritoneal endometriosis in humans (28). Nine hyperprolactinemic patients with endometriosis "requiring a first surgical intervention and benefiting from a second-look laparoscopy" were evaluated. During the first surgical procedure, lesions of endometriosis were identified. In each patient, one-half of the lesions were removed, whereas the remaining one-half was labeled. Following laparoscopy, the participants received quinagolide (25–75 μg per day) for 18–20 weeks. After 20 weeks, a second surgical procedure was performed. The number of endometriosis lesions was again quantified, and any identified remaining lesions were surgically excised. The investigators reported that quinagolide induced a 69.5% reduction in the size of the lesions, with 35% of these vanishing completely (28). Histology showed tissue degeneration as well as the downregulation of VEGF/VEGF-R2 and 3 proangiogenic cytokines, but no patient outcomes (such as pain) were evaluated. We tested the hypothesis that the level of serum angiogenic markers decreases over time in patients treated with nonhormonal therapy, cabergoline, compared with those who receive hormonal therapy, NETA. Although limited by our small sample size, we demonstrated a trend toward decreased VEGF-R1 levels over time in subjects receiving cabergoline compared with those receiving NETA.

Our current pilot study represents the first step in building upon these previous results to determine if cabergoline also leads to symptomatic improvement. Our pilot data suggest that cabergoline is at least as effective as NETA in decreasing pelvic pain severity, improving pain relief, and maintaining normal functioning. The use of pain medication was lower in the participants receiving cabergoline as well. The side effects were minimal and similar between the 2 groups. Our symptom questionnaire was developed to standardize the reporting of side effects. However, we acknowledge that this tool may have led to increased reporting of symptoms by our participants. Additionally, it is well known that endometriosis overlaps with other chronic pain conditions, such as irritable bowel syndrome, migraines, and fibromyalgia. Many of the symptoms reported were not unexpected and may have been due to other medical conditions, including endometriosis itself, rather than related to study medication use. The investigators identified just 2 CTCAE grade 2 adverse events. No serious adverse events occurred, and the safety parameters measured remained within the normal range. Cabergoline may be an alternative to opiate therapies that are

currently employed, unsuccessfully, for the long-term management of endometriosis-related chronic pain (56, 57).

The study's limitations should be acknowledged. Given that this investigation was a pilot study, our extremely small sample size precluded robust statistical analyses. We used these results to inform a larger, prospective study of cabergoline, which is currently underway. We found that a positive response to the question "Since last visit, have you had changes in vaginal bleeding?" was more common in women randomized to the cabergoline group (elicited at 41% of participant visits) than in those randomized to the NETA group (elicited at 24% of participant visits). In addition, the patients were somewhat reluctant to enroll in a cabergoline-only trial arm because of concerns for undesired pregnancy and unscheduled vaginal bleeding. Based on these results, our larger trial investigated the use of cabergoline as an adjunct to hormonal therapy.

CONCLUSION

Endometriosis is the most common reproductive disease observed in young women, often leading to debilitating chronic pelvic pain and impaired quality of life. Safe, effective, long-term adjunct treatments are lacking for patients who do not respond to the current standard of care or for those who request nonhormonal therapy. Because the growth of new tissue requires angiogenesis, blood vessel growth is an attractive target for endometriosis therapy. Cabergoline represents an attractive VEGF pathway inhibitor because of its side effect profile. This pilot study suggests that it is an effective therapeutic option for women with chronic pain due to endometriosis. We plan to build upon this investigation and conduct larger randomized trials of cabergoline, advancing research on the best treatments for endometriosis—particularly disease resistant to, or patients seeking alternatives to, hormonal therapies.

REFERENCES

1. Zondervan KT, Becker CM, Missmer SA. Endometriosis. N Engl J Med 2020;382:1244–56.
2. Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. Lancet 2021;397:839–52.
3. ACOG Committee Opinion. Number 310, April 2005. Endometriosis in adolescents. Obstet Gynecol 2005;105:921–7.
4. Nothnick W, Alali Z. Recent advances in the understanding of endometriosis: the role of inflammatory mediators in disease pathogenesis and treatment. F1000Research 2016;5.
5. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 2011;96:366–73.
6. Hoshiai H, Ishikawa M, Sawatari Y, Noda K, Fukaya T. Laparoscopic evaluation of the onset and progression of endometriosis. Am J Obstet Gynecol 1993;169:714–9.
7. Thomas EJ, Cooke ID. Impact of gestrinone on the course of asymptomatic endometriosis. Br Med J (Clin Res Ed) 1987;294:272–4.
8. Ozkan S, Arici A. Advances in treatment options of endometriosis. Gynecol Obstet Invest 2009;67:81–91.
9. Youngster M, Laufer MR, Divasta AD. Endometriosis for the primary care physician. Curr Opin Pediatr 2013;25:454–62.
10. Gallagher JS, Missmer SA, Hornstein MD, Laufer MR, Gordon CM, DiVasta AD. Long-term effects of gonadotropin-releasing hormone agonists and add-back in adolescent endometriosis. J Pediatr Adolesc Gynecol 2018;31:376–81.
11. Parazzini F, Fedele L, Busacca M, Falsetti L, Pellegrini S, Venturini PL, et al. Postsurgical medical treatment of advanced endometriosis: results of a randomized clinical trial. Am J Obstet Gynecol 1994;171:1205–7.
12. Hornstein MD, Hemmings R, Yuzpe AA, Heinrichs WL. Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis. Fertil Steril 1997;68:860–4.
13. Telimaa S, Puolakka J, Rönnberg L, Kauppila A. Placebo-controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis. Gynecol Endocrinol 1987;1:13–23.
14. Becker CM, Gattrell WT, Gude K, Singh SS. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertil Steril 2017;108:125–36.
15. Shifren JL, Tseng JF, Zaloudek CJ, Ryan IP, Meng YG, Ferrara N, et al. Ovarian steroid regulation of vascular endothelial growth factor in the human endometrium: implications for angiogenesis during the menstrual cycle and in the pathogenesis of endometriosis. J Clin Endocrinol Metab 1996;81:3112–8.
16. Asante A, Taylor RN. Endometriosis: the role of neuroangiogenesis. Annu Rev Physiol 2011;73:163–82.
17. Taylor RN, Hummelshoj L, Stratton P, Vercellini P. Pain and endometriosis: etiology, impact, and therapeutics. Middle East Fertil Soc J 2012;17:221–5.
18. Walsh DA, Pearson CI. Angiogenesis in pathogenesis of inflammatory joint and lung diseases. Arthritis Res 2001;3:147–53.
19. Nap AW, Griffioen AW, Dunselman GA, Bouma-Ter Steege JC, Thijssen VL, Evers JL, et al. Antiangiogenesis therapy for endometriosis. J Clin Endocrinol Metab 2004;89:1089–95.
20. Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med 2008;358:1129–36.
21. Elice F, Rodeghiero F. Side effects of anti-angiogenic drugs. Thromb Res 2012;129:S50–3.
22. Basu S, Sarkar C, Chakroborty D, Nagy J, Mitra RB, Dasgupta PS, et al. Ablation of peripheral dopaminergic nerves stimulates malignant tumor growth by inducing vascular permeability factor/vascular endothelial growth factor-mediated angiogenesis. Cancer Res 2004;64:5551–5.
23. Basu S, Nagy JA, Pal S, Vasile E, Eckelhoefer IA, Bliss VS, et al. The neurotransmitter dopamine inhibits angiogenesis induced by vascular permeability factor/vascular endothelial growth factor. Nat Med 2001;7:569–74.
24. Robert E, Musatti L, Piscitelli G, Ferrari CI. Pregnancy outcome after treatment with the ergot derivative, cabergoline. Reprod Toxicol 1996;10:333–7.
25. Ricci E, Parazzini F, Motta T, Ferrari CI, Colao A, Clavenna A, et al. Pregnancy outcome after cabergoline treatment in early weeks of gestation. Reprod Toxicol 2002;16:791–3.
26. Colao A, Abs R, Bárcena DG, Chanson P, Paulus W, Kleinberg DL. Pregnancy outcomes following cabergoline treatment: extended results from a 12-year observational study. Clin Endocrinol (Oxf) 2008;68:66–71.
27. Delgado-Rosas F, Gómez R, Ferrero H, Gaytan F, Garcia-Velasco J, Simón C, et al. The effects of ergot and non-ergot-derived dopamine agonists in an experimental mouse model of endometriosis. Reproduction 2011;142:745–55.
28. Gómez R, Abad A, Delgado F, Tamarit S, Simón C, Pellicer A, et al. Effects of hyperprolactinemia treatment with the dopamine agonist quinagolide on endometriotic lesions in patients with endometriosis-associated hyperprolactinemia. Fertil Steril 2011;95:882–8.e1.
29. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.
30. Howard FM. Laparoscopic evaluation and treatment of women with chronic pelvic pain. J Am Assoc Gynecol Laparosc 1994;1:325–31.

31. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain 2004;20:309–18.
32. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–38.
33. Beck AT, Brown G, Steer RA. Beck depression inventory II manual. San Antonio, TX: The Psychological Corporation; 1996.
34. Dworkin RH, Corbin AE, Young JP, Sharma U, LaMoreaux L, Bockbrader H, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003;60:1274–83.
35. Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006;67:1411–20.
36. Kashikar-Zuck S, Flowers SR, Claar RL, Guite JW, Logan DE, Lynch-Jordan AM, et al. Clinical utility and validity of the functional disability inventory among a multicenter sample of youth with chronic pain. Pain 2011;152:1600–7.
37. Pupo-Nogueira A, de Oliveira RM, Petta CA, Podgaec S, Dias JA, Abrao MS. Vascular endothelial growth factor concentrations in the serum and peritoneal fluid of women with endometriosis. Int J Gynaecol Obstet 2007;99:33–7.
38. Gagne D, Gagné D, Pagé M, Robitaille G, Hugo P, Gosselin D. Levels of vascular endothelial growth factor (VEGF) in serum of patients with endometriosis. Hum Reprod 2003;18:1674–80.
39. Othman EE, Hornung D, Salem HT, Khalifa EA, El-Metwally TH, Al-Hendy A. Serum cytokines as biomarkers for nonsurgical prediction of endometriosis. Eur J Obstet Gynecol Reprod Biol 2008;137:240–6.
40. Xavier P, Belo L, Beires J, Rebelo I, Martinez-de-Oliveira J, Lunet N, et al. Serum levels of VEGF and TNF-alpha and their association with C-reactive protein in patients with endometriosis. Arch Gynecol Obstet 2006;273:227–31.
41. Vodolazkaia A, El-Aalamat Y, Popovic D, Mihalyi A, Bossuyt X, Kyama CM, et al. Evaluation of a panel of 28 biomarkers for the non-invasive diagnosis of endometriosis. Hum Reprod 2012;27:2698–711.
42. Cho SH, Oh YJ, Nam A, Kim HY, Park JH, Kim JH, et al. Evaluation of serum and urinary angiogenic factors in patients with endometriosis. Am J Reprod Immunol 2007;58:497–504.
43. Ferrero S, Ragni N, Remorgida V. Antiangiogenic therapies in endometriosis. Br J Pharmacol 2006;149:133–5.
44. McLaren J, Prentice A, Charnock-Jones DS, Smith SK. Vascular endothelial growth factor (VEGF) concentrations are elevated in peritoneal fluid of women with endometriosis. Hum Reprod 1996;11:220–3.
45. Kalu E, Sumar N, Giannopoulos T, Patel P, Croucher C, Sherriff E, et al. Cytokine profiles in serum and peritoneal fluid from infertile women with and without endometriosis. J Obstet Gynaecol Res 2007;33:490–5.
46. Rathore N, Kriplani A, Yadav RK, Jaiswal U, Netam R. Distinct peritoneal fluid ghrelin and leptin in infertile women with endometriosis and their correlation with interleukin-6 and vascular endothelial growth factor. Gynecol Endocrinol 2014;30:671–5.
47. Kianpour M, Nematbakhsh M, Ahmadi SM, Jafarzadeh M, Hajjarian M, Pezeshki Z, et al. Serum and peritoneal fluid levels of vascular endothelial growth factor in women with endometriosis. Int J Fertil Steril 2013;7:96–9.
48. Wang H, Gorpudolo N, Li Y, Feng D, Wang Z, Zhang Y. Elevated vascular endothelia growth factor-A in the serum and peritoneal fluid of patients with endometriosis. J Huazhong Univ Sci Technolog Med Sci 2009;29:637–41.
49. Küpker W, Schultze-Mosgau A, Diedrich K. Paracrine changes in the peritoneal environment of women with endometriosis. Hum Reprod Update 1998;4:719–23.
50. Novella-Maestre E, Carda C, Ruiz-Sauri A, Garcia-Velasco JA, Simon C, Pellicer A. Identification and quantification of dopamine receptor 2 in human eutopic and ectopic endometrium: a novel molecular target for endometriosis therapy. Biol Reprod 2010;83:866–73.
51. Santoro L, D'Onofrio F, Flore R, Gasbarrini A, Santoliquido A, D'Onofrio F, et al. Endometriosis and atherosclerosis: what we already know and what we have yet to discover. Am J Obstet Gynecol 2015;213:326–31.
52. Donnez J, Binda MM, Donnez O, Dolmans MM. Oxidative stress in the pelvic cavity and its role in the pathogenesis of endometriosis. Fertil Steril 2016;106:1011–7.
53. Mu F, Harris HR, Rich-Edwards JW, Hankinson SE, Rimm EB, Spiegelman D, et al. A prospective study of inflammatory markers and risk of endometriosis. Am J Epidemiol 2018;187:515–22.
54. Mahnke JL, Dawood MY, Huang JC. Vascular endothelial growth factor and interleukin-6 in peritoneal fluid of women with endometriosis. Fertil Steril 2000;73:166–70.
55. Novella-Maestre E, Carda C, Noguera I, Ruiz-Saurí A, García-Velasco JA, Simón C, et al. Dopamine agonist administration causes a reduction in endometrial implants through modulation of angiogenesis in experimentally induced endometriosis. Hum Reprod 2009;24:1025–35.
56. As-Sanie S, Soliman AM, Evans K, Erpelding N, Lanier R, Katz NP. Healthcare utilization and cost burden among women with endometriosis by opioid prescription status in the first year after diagnosis: a retrospective claims database analysis. J Med Econ 2020;23:371–7.
57. Steele A. Opioid use and depression in chronic pelvic pain. Obstet Gynecol Clin North Am 2014;41:491–501.