Relief of Idiopathic Subjective Tinnitus

Is Gabapentin Effective?

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Objective: To assess the therapeutic benefit of gabapentin (Neurontin) for subjective idiopathic troublesome tinnitus.

Design: An 8-week, double-blind, randomized clinical trial.

Setting: Academic otolaryngology clinic in St Louis, Mo.

Subjects: One hundred thirty-five subjects with severe idiopathic subjective tinnitus of 6 months' duration or longer.

Intervention: Gabapentin, at a maintenance dosage of 900 to 3600 mg/d for 8 weeks, or lactose placebo.

Main Outcome Measure: Change in the Tinnitus Handicap Inventory score from baseline to the study end point.

Results: The overall change in the Tinnitus Handicap Inventory score for the entire cohort from baseline to week 8 was 11.2; the change among the 59 subjects randomized to the gabapentin arm was 11.3 and the change among the 56 subjects in the placebo arm was 11.0. The difference was 0.03 (95% confidence interval, -5.5 to 6.2; \( P = .91 \)).

Conclusion: Gabapentin is no more effective than placebo for the relief of idiopathic subjective tinnitus.

Trial Registration: clinicaltrials.gov Identifier: NCT00317850

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Tinnitus is the perceived sensation of sound without actual acoustic stimulation. Approximately 40 million people in the United States experience chronic tinnitus, and 10 million of these consider their tinnitus to be a significant problem.1 Although there are many theories about the basic mechanisms underlying subjective tinnitus,2 the precise physiological process remains unknown. The available evidence, based on clinical observation and electrophysiologic studies3-6 during the past decade, suggests that tinnitus is associated with disturbances in spontaneous neural activity in the auditory system (central-origin hypothesis). These abnormalities include increases in spontaneous activity (hyperactivity), changes in the timing of neural discharges (ie, the temporal firing properties of neurons), and an increase in the bursting activity of neurons.

Tonndorf7 was the first to suggest an analogy between the origin of chronic tinnitus and intractable pain. He hypothesized that severe tinnitus may represent a form of allodynia, which is a painful sensation of normally innocuous stimulation of the skin. Folmer et al8 also investigated the similarities between patients who experienced chronic tinnitus and patients who experienced chronic pain. They found that the severity of chronic tinnitus is correlated with the severity of insomnia, anxiety, and depression and that these relationships are the same for patients with chronic pain. They suggested that tinnitus be viewed as a form of phantom auditory pain. They formulated treatment strategies, based on a chronic pain model, that were likely to be effective for chronic tinnitus.

Recently, a published case report described a patient who presented to a chronic pain clinic with a 10-month history of tinnitus.10 The patient was prescribed a 2-week course of gabapentin (Neurontin; Parke-Davis, Morris Plains, NJ). Within 24 hours of starting drug therapy, the patient's tinnitus ceased. However, after 2 weeks, the patient's supply of gabapentin was depleted and his tinnitus immediately returned. The patient re-
started gabapentin treatment and maintained a good response for more than 2 years.

Bauer and Brozoski evaluated the effectiveness of gabapentin in a placebo-controlled single-blind clinical trial in 2 cohorts of adult subjects with tinnitus—those with and those without evidence of acoustic trauma. Acoustic trauma was defined as having a “notch” between 3 and 6 kHz in the pure-tone average audiogram. The investigators developed an Objective Stimulus Loudness Match and used this with the Tinnitus Handicap Questionnaire and other measures to assess changes in tinnitus. They found no significant overall effect of gabapentin on psychoacoustic tinnitus loudness or Tinnitus Handicap Questionnaire responses in either cohort of subjects with tinnitus. They also reported no significant difference between the 2 trauma groups in the number of subjects who reported improvement of 20 dB or better—6 (30%) of 20 subjects in the trauma group and 3 (16%) of 19 in the non-trauma group (Yates $\chi^2=0.452; P=.5$).

The goal of this study was to assess the role of gabapentin in the treatment of tinnitus. In particular, we wanted to investigate whether the findings of therapeutic benefit with gabapentin reported in some of the published literature could be replicated in a randomized double-blind trial.

STUDY DESIGN AND POPULATION

We conducted a double-blind placebo-controlled randomized clinical trial. The study was approved by the Washington University Human Studies Committee (HSC 02-0717), St Louis, Mo, and is listed in the ClinicalTrials.gov database. Subjects were primarily recruited through the Washington University Department of Otolaryngology—Head and Neck Surgery and the Volunteer for Health program. Subjects were required to be 18 to 70 years of age and have tinnitus of 6 months’ duration or longer and of sufficient severity to disrupt daily activities. The Tinnitus Handicap Inventory (THI) is a validated measure of the degree of handicap due to tinnitus in which scores range from 0 to 100; scores of 20 or above indicate clinically significant psychological distress. The Beck Depression Inventory is a validated measure of the degree of depression in which scores range from 0 to 100; scores of 20 or above indicate clinically significant depression.

METHODS

STUDY DESIGN AND POPULATION

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RANDOMIZATION AND PROTOCOL

Study eligibility was determined and informed consent was obtained during the subject’s first visit. Following the baseline evaluation, subjects were sequentially randomized in a double-blind fashion, according to a computer-generated random code, to receive placebo (lactose) or gabapentin (300 mg per capsule) in identical blue capsules. The research pharmacist at Barnes-Jewish Hospital, St Louis, maintained the randomization schedule and prepared the gabapentin and placebo capsules for the entire study.

TRIAL MANAGEMENT AND DEFINITIONS

Otologic evaluation was performed at the time of enrollment by a board-certified otolaryngologist (J.F.P. or R.A.C.). Pure-tone, air, and bone conduction thresholds; speech reception threshold; and speech recognition studies were performed by licensed and certified audiologists at treatment initiation. No attempt was made to match loudness of tinnitus with severity because several studies have demonstrated that the matched loudness of tinnitus is not correlated with its severity.

During the first 4 weeks of the study, subjects randomized to the gabapentin arm received gradually titrated dosages of gabapentin (week 1, 900 mg/d; week 2, 1800 mg/d; week 3, 2700 mg/d; and week 4, 3600 mg/d). The medications were distributed in 4 separate vials representing each of the 4 weeks of the titration period. All subjects were provided an equal number of capsules and instructed to follow a dosing schedule of 3 times per day. Because tinnitus severity can fluctuate spontaneously, all subjects’ dosages were titrated to a maximum dose of 3600 mg/d, regardless of any effect achieved at lower dosages. If intolerable adverse reactions occurred, the dosage was decreased in 1-dose (ie, 300-mg) steps until the drug could be tolerated. The dose established during the titration period was maintained throughout the fixed-dose period. Matching placebo capsules were similarly administered to subjects randomized to the placebo arm.

Subjects were contacted via telephone by the research assistant (J.F.) at the end of weeks 1 and 3. The purposes of these telephone calls were to query the subjects about adverse effects and remind them of their week 4 visit. Subjects were also asked to maintain daily diaries of tinnitus symptoms and adverse effects possibly related to gabapentin treatment. The medications were distributed in 4 separate vials representing the 4 weeks of the fixed-dose period. The research assistant contacted the subjects at the end of week 6 to query them about compliance and maintenance of daily diaries. At the completion of the study (week 8), a sufficient supply of gabapentin and instructions for tapering off gabapentin therapy were provided to subjects who wished to discontinue it. This taper-off protocol was required because the abrupt disuse of gabapentin may lead to the lowering of seizure thresholds.

The degree of compliance with medication was determined by performing a pill count. At the return visits (weeks 4 and 8), the research assistant counted the number of pills remaining in each of the weekly vials and calculated the degree of compliance. The subjects were then asked open-ended questions regarding compliance.

The safety of gabapentin was assessed using the adverse events data form (occurrence, intensity, and relationship to study drug) and, when appropriate, the results of physical examinations performed by one of us (J.F.P. or R.A.C.) or the patient’s primary or specialty physician. The study physicians
(J.F.P. and R.A.C.) performed the exit interview for all enrolled subjects. The degree of blinding was assessed at the end of the study by asking the subject and the physician to identify which product, gabapentin or placebo, they believed was received.

At trial completion and before breaking the blind, subjects were asked to record their global satisfaction with the treatment received using the Patient Global Impression of Change questionnaire. The Patient Global Impression of Change is a 7-point ordinal scale with anchors of very much improved and very much worse on which subjects rate their change in overall tinnitus. Subjects were also asked whether they would recommend the treatment they received to a friend. The primary efficacy variable was the change in the THI score from weeks 0 to 8 between the 2 treatment arms. Secondary efficacy variables were the Patient Global Impression of Change score and changes in the Brief Symptom Inventory and Beck Depression Scale scores.

STATISTICAL ANALYSES

All sample size and power computations were based on 2-sided tests at the α = .05 level of significance and were based on the results from a preliminary open-label study of 19 subjects (J.F.P., R.A.C., and E.S., unpublished data, 2002). In that study, the mean THI score decreased from a baseline value of 44 to 28 (SD, 26). Assuming that a similar result would be found in the proposed study, computations indicated that 42 subjects with evaluable data per group would yield a power of 0.80. 56 per group would yield a power of 0.90, and 69 per group would yield a power of 0.95. The investigators anticipated that 10% of the subjects would drop out of the study and that their data would not be analyzable because they provided no follow-up data. Thus, to achieve statistical power values of 0.80, 0.90, and 0.95, it was necessary to inflate the numbers by 10% and to randomize 47, 62, and 77 subjects, respectively, per group. Based on these considerations, the estimated target sample size of 80 randomized subjects per group would yield a statistical power of approximately 0.95.

The primary analysis was a modified intention-to-treat analysis defined as including all randomized subjects who received at least 1 dose of study medication during the fixed-dose period and who provided at least 1 follow-up efficacy assessment. Data were analyzed using SAS statistical software (version 8.02; SAS Institute Inc, Cary, NC). An initial set of analyses used 2-tailed t tests and χ² tests to compare baseline characteristics of the 2 treatment groups to ensure that randomization yielded the anticipated between-group comparability. Because outcome measures were evaluated at 3 time points (weeks 0, 4, and 8), the primary analysis was a repeated-measures analysis of variance. This allowed the comparison between the change from baseline (week 0) to trial completion (week 8) in the control group with the corresponding change in the gabapentin group. In addition, 2-factor repeated-measures analyses of variance were performed with age, sex, race, duration of tinnitus, and Beck Depression Inventory score combined at a time with treatment. Because the primary analysis involved changes from baseline to 8 weeks, standard errors generated by the analyses of covariance were used to compute 95% confidence intervals (CIs) on between-group differences in the change from the first to the last measurement. These analytic strategies were applied to the change in the THI score, the primary end point, as well as to all of the secondary end points.

The clinically significant difference in the change between the pretreatment and posttreatment THI scores was determined according to the method of Newman et al¹⁸ to be 20. This value was derived from analysis of the 95% CIs around the difference value. Subjects who achieved this degree of change (ie, ≥20) were classified as having a treatment success. The difference of 20 on the THI score between the amount of change in the gabapentin and placebo groups (ie, the difference between groups of the change within groups) was defined as clinically significant.

To our knowledge, there have been no reports of sex and/or race/ethnicity differences in the impact of gabapentin on tinnitus. There are no known biological reasons why gabapentin would have different effects based on sex and/or race/ethnicity. Therefore, no clinically important sex and/or race/ethnicity differences in the impact of gabapentin on tinnitus in this study were anticipated. However, analyses were performed to determine whether there are any sex or race (black-white) differences.

All data analyses were accompanied by routine assessments aimed at ensuring that the distributional properties of variables satisfied the criteria that are necessary for the particular analytic strategy. Thus, the normality and equal variance assumptions were assessed to ensure that the t test was a valid analytic procedure. Similarly, the appropriateness of the analyses of covariance was confirmed by evaluating the normality of regression residuals. When conditions were not satisfied, data transformations were explored and, when appropriate transformations could not be found, nonparametric methods were used.

RESULTS

DESCRIPTION OF THE POPULATION

Of the 1028 subjects screened, 359 were eligible and 135 were enrolled (Figure 1). The major reason for ineligibility was a score on the THI below 38. Of the 135 who enrolled, 115 completed the study. Lack of results and development of adverse effects were the 2 main reasons expressed for dropout.

The mean ± SD age in years of our sample was 57.0 ± 8.2 years; for subjects in the gabapentin group, 56.9 ± 9.0 years; and for subjects in the placebo group, 58.2 ± 7.3 years (P = .67) (Table 1). There were no significant differences between subjects randomized to gabapentin or placebo except for loudness of tinnitus. Subjects randomized to receive gabapentin were less likely to report their tinnitus as loud.

Of 59 subjects who were randomized to gabapentin, 43 (73%) were compliant throughout the study without missing a dose. The 16 remaining subjects (27%) reported missing 1 to 3 doses during the 8-week trial. Of the 56 subjects who were randomized to placebo, 48 (86%) were compliant throughout the study without missing a dose. The 8 remaining subjects (14%) reported missing 1 to 3 doses. The differences in compliance between the 2 groups of subjects were not statistically significant (P = .23).

DEGREE OF BLINDING

Of the 59 subjects who were randomized to gabapentin, 20 (34%) guessed they were randomized to gabapentin; of the 56 subjects who were randomized to placebo, 8 (14%) guessed that they were randomized to gabapentin (P = .01).
Discontinued Study

Most of the subjects (n = 51 [86%]) randomized to gabapentin were successfully titrated to a dosage of 3600 mg/d in the first 4 weeks and were fixed at that dosage for the duration of the study. Four (7%) achieved a maintenance dosage of 2700 mg/d; 3 (5%), 1800 mg/d; and 1 (2%), 900 mg/d. Of the 56 subjects randomized to placebo, 50 (89%) were able to tolerate 4 placebo pills each day, and 2 (3%) each achieved maintenance dosages of 2700, 1800, and 900 mg/d.

ADVERSE EFFECTS

Nine (7%) of the 135 subjects withdrew from participation owing to adverse effects. Three of these subjects experienced nausea, 2 reported weight gain, 2 reported sleep disturbance, and 2 reported dizziness. All adverse effects ceased on discontinuation of the study medication. Withdrawal from the study was evenly distributed across the gabapentin and placebo groups. Of the 70 subjects initially randomized to gabapentin, 11 (16%) withdrew from the study; of the 65 initially randomized to placebo, 9 (14%) withdrew from the study.

CHANGE IN THI SCORE

At baseline, the mean THI score for subjects randomized to gabapentin was 49.5; for subjects randomized to placebo, 51.8. At week 8, the mean THI score for subjects randomized to gabapentin was 38.2; for those randomized to placebo, 40.7 (Figure 2). The change in the THI score from baseline to week 8 for the gabapentin group was 11.3; for the placebo group, 11.0. The difference in the change in the THI score from baseline to week 8 between the gabapentin and placebo groups was 0.3 (95% CI, −5.5 to 6.2). This difference of 0.3 was not significantly different from 0 (P = .91), and the upper bound of the 95% CI is well below the minimally important difference of 20 as stated by Newman et al. Thus, even the greatest amount of difference suggested by the data would not be clinically significant. In the gabapentin group, 22 subjects (37%) achieved a change of 20 points or greater on their THI scores during the course of the trial whereas, in the placebo group, 18 (32%) achieved a similar change. This difference in the proportion of subjects who achieved a clinically meaningful change in the THI score was not statistically significant (P = .56).

A repeated-measures analysis was performed on the THI scores at weeks 0, 4, and 8 for the 2 treatment groups overall and by important demographic and clinical features (Table 2). This analysis showed no significant difference in the THI scores at weeks 0, 4, and 8 between the gabapentin and placebo groups overall. There was no significant between-subject effect for age groups (P = .61); however, univariate analyses for within-subject effects showed that there was a significant difference between treatment groups within the 3 different age groups across the trajectory of the study (P = .04). In addition, there was a significant change in the THI score at weeks 0, 4, and 8 between the gabapentin and placebo groups among subjects with normal hearing (Table 2). Among subjects with normal hearing who received gabapentin, there was a 21.40-point change in THI score from weeks 0 to 8. Among subjects with normal hearing who received placebo, there was a 1.75-point change in THI score. The difference in the change in THI score between the gabapentin and placebo arms was 19.7 (P = .005).

SECONDARY OUTCOME MEASURES

Subjects were asked to describe their overall degree of life disturbance due to tinnitus, their overall impression of change in tinnitus, and whether they would recommend the product they received to a friend (Table 3). There were no significant differences in responses to these 3 questions between subjects in the 2 treatment arms. In the gabapentin group, 46% of subjects reported that they were very bothered or bothered a lot at baseline and 39% reported that they were very bothered or bothered a lot at week 8. This difference (−7%; 95% CI, −19% to 6%) was not statistically significant (McNemar χ² = 3.56; P = .06). In the placebo group, 53% of the subjects reported that they were very bothered or bothered a lot at baseline, and 41% of the subjects reported that they were very bothered or bothered a lot at week 8. This difference (−14%; 95% CI, −28% to 0.6%) was also not statistically significant (McNemar χ² = 3.56; P = .06). Based on these secondary outcome measures, there were no differences in response among normal hearing adults randomized to the 2 different treatment arms.
This clinical trial assessed the therapeutic impact of gabapentin in the treatment of subjective idiopathic tinnitus. The results demonstrate that gabapentin was no more effective than placebo among a group of patients with tinnitus. In both the gabapentin and placebo treatment arms, subjects demonstrated a significant reduction in severity of tinnitus as measured by the THI score during the 8 weeks of the study. The greatest amount of improvement in tinnitus for both groups was experienced during the first 4 weeks of the study. The difference in the change in the THI score during the 8 weeks of the study (baseline to week 8) was not significantly different between the 2 groups, and the upper bound of the 95% CI did not exceed the value of the minimum important difference. There were no differences across groups in the global rating of tinnitus bother, global improvement, or whether the subject would recommend similar treatment to a friend.
There are many different treatments for tinnitus. Jastreboff and Jastreboff describe tinnitus retraining therapy based on the neurophysiologic model of tinnitus that they have popularized. Bartnik et al evaluated an 18- to 24-month period of tinnitus retraining therapy in 108 patients with tinnitus and/or hyperacusis. They found a significant improvement in about 70% of patients with tinnitus only and in about 90% of patients with tinnitus and subjective hearing loss after 1 year of therapy. Andersson and Lyttkens performed a meta-analysis on psychological treatment of tinnitus. The outcomes of 18 studies, involving more than 700 subjects, were included and coded. Studies that examined cognitive/cognitive-behavioral treatment, relaxation, hypnosis, biofeedback, educational sessions, and problem solving were included. They concluded that psychological treatment for tinnitus is effective, but that aspects such as depression and sleep problems may need to be targeted in future studies.

A systematic review of the literature of randomized clinical trials by Dobie found 69 clinical trials of various drugs, psychotherapy, maskers, acupuncture, hypnosis, and other treatments. He concluded that none of the treatments were able to eliminate tinnitus more fre-
though less compelling, clinical evidence supports its use similar to the tricyclic antidepressants. Consistent, al-
pentin at dosages of 2400 to 3600 mg/d has an efficacy.

GABA uptake or degradation. Preclinical studies have into GABA or a GABA agonist, and is not an inhibitor of

clinical trials were noted, such as small sample sizes and

GABA receptors, is not converted metabolically

and others. Gabapentin is now widely used for neuro-
pathic pain because it is generally well tolerated and easily titrated, has few drug interactions, and does not re-
quire laboratory monitoring. The usual effective total daily
dose is 900 to 3600 mg, administered in 3 divided doses per day; higher doses may be needed.

Bauer and Brozoski developed an animal psycho-
physical model to reflect several features of tinnitus ob-
served in humans and to test the impact of gabapentin. Chronic tinnitus was induced in rats by a single intense unilateral exposure to noise. The tinnitus was measured using a psychophysical procedure, which required the animals to discriminate between auditory test stimuli consisting of tones, noise, and silence. The tinnitus was found to persist and intensify during 17 months of testing. Finally, the tinnitus was reversibly attenuated by treatment with gabapentin.

In human use of gabapentin for tinnitus, Zapp reported a case of the relief of tinnitus in a patient with chronic pain. In a placebo-controlled clinical trial, Bauer and Brozoski did not find gabapentin effective overall as measured by psychoacoustically determined or patient-based ratings. Nor did they find gabapentin effective over-
all within the subgroup of acoustic trauma or non-
trauma patients. They reported effectiveness among acoustic trauma patients at 2 of 4 daily dosage levels when the acoustic trauma patients were divided into high- and low-level responders. However, several methodological shortcomings render the authors’ interpretation of these data as evidence of the effectiveness of gabapentin in adults with a history of acoustic trauma as severely flawed. The methodological shortcomings include analysis of the treatment effect within groups of patients defined by treat-
ment effect, failure to describe the subgroup analysis be-
tween the study (ie, use of post hoc analysis), problems of false-positive findings with multiple comparisons (ie, 6 different drug dose treatment levels were compared), and small sample size.

In the present study, we found that subjects with normal hearing who received gabapentin showed a sta-
tistically significant improvement in tinnitus, as mea-
sured by the THI score, whereas subjects who received placebo showed no change in the THI score. However, the response to gabapentin that we found among the normal-hearing subjects based on the THI score was not supported by other outcome measures such as the global rating of response or satisfaction with care. Thus, although this effect of gabapentin among normal-hear-
ing adults may be real, we believe the response to gaba-
pentin, as measured by the THI score, does not reflect a true effect.

The degree of success of blinding was assessed by analy-
zing the percentage of subjects who correctly identi-
fied the arm to which they had been randomized. In both treatment arms, a greater number of patients believed they had been randomized to placebo, and patients random-
ized to placebo were much more likely than patients ran-
domized to gabapentin to correctly identify their assign-
ment. Perhaps this is because most of the subjects who received gabapentin experienced no therapeutic effect. Those who received gabapentin and thought they were

| Table 3. Relationship Between Secondary Outcome Measures and Treatment at Week 8 |
|---------------------------------|---------------------|------------------|
| Outcome Measures | Treatment Group, No. (%) of Subjects | Difference, P Value |
| Overall life disturbance at study completion | Gabapentin | Placebo | .20 |
| Not bothered | 1 (2) | 2 (4) |
| Some | 15 (25) | 5 (9) |
| More than some | 20 (34) | 26 (46) |
| A lot | 22 (37) | 21 (38) |
| Very bothered | 1 (2) | 2 (4) |
| Global improvement change in tinnitus severity at study completion | | .16 |
| Very much worse | 1 (2) | 3 (5) |
| Somewhat worse | 6 (10) | 1 (2) |
| Minimally worse | 1 (2) | 4 (7) |
| Normal | 40 (67) | 44 (77) |
| Minimally better | 7 (12) | 3 (5) |
| Somewhat better | 3 (5) | 2 (4) |
| Very much better | 1 (2) | 0 |
| Recommendation of study drug to friends with tinnitus | | .20 |
| Definitely no | 12 (20) | 8 (14) |
| Maybe no | 9 (15) | 5 (9) |
| Maybe yes | 4 (7) | 3 (5) |
| Definitely yes | 11 (19) | 6 (11) |
| Unsure | 23 (39) | 35 (61) |

*Because of rounding, percentages may not total 100.
receiving gabapentin generally experienced adverse effects. It was determined through multivariate logistic regression that adverse effects had the greatest influence on a patient’s guess. It was also demonstrated that patients who correctly thought they were randomized to gabapentin had a greater, although not statistically significant, change in their THI score. Investigators in the future should be aware that patients guessing gabapentin are much more common in the gabapentin arm than in the placebo arm. This may conceivably lead to some form of a perception of an effect.

Troublesome tinnitus is a common health problem, and treatment options for these subjects are quite limited. Despite basic scientific evidence, a case report of success in treatment of tinnitus with gabapentin, and clinical similarities between tinnitus and neuropathic pain, we did not find that gabapentin was clinically efficacious for the treatment of tinnitus. To date, the US Food and Drug Administration has not approved any drug for the treatment of tinnitus. Future clinical trials should continue to explore the effect of other centrally acting drugs. The findings from such research can have a significant effect on health for a large number of Americans.

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Author Contributions: Drs Piccirillo, Chole, and Spitznagel had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Piccirillo, Chole, and Spitznagel. Acquisition of data: Piccirillo, Finnell, and Spitznagel. Analysis and interpretation of data: Piccirillo, Vlahiotis, and Spitznagel. Drafting of the manuscript: Piccirillo, Finnell, Vlahiotis, Chole, and Spitznagel. Critical revision of the manuscript for important intellectual content: Piccirillo, Vlahiotis, and Spitznagel. Statistical analysis: Vlahiotis and Spitznagel. Obtained funding: Piccirillo and Chole. Study supervision: Piccirillo and Chole.

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