ARTICLE

Effect of Honey, Dextromethorphan, and No Treatment on Nocturnal Cough and Sleep Quality for Coughing Children and Their Parents

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Objectives: To compare the effects of a single nocturnal dose of buckwheat honey or honey-flavored dextromethorphan (DM) with no treatment on nocturnal cough and sleep difficulty associated with childhood upper respiratory tract infections.

Design: A survey was administered to parents on 2 consecutive days, first on the day of presentation when no medication had been given the prior evening and then the next day when honey, honey-flavored DM, or no treatment had been given prior to bedtime according to a partially double-blinded randomization scheme.

Setting: A single, outpatient, general pediatric practice.

Participants: One hundred five children aged 2 to 18 years with upper respiratory tract infections, nocturnal symptoms, and illness duration of 7 days or less.

Intervention: A single dose of buckwheat honey, honey-flavored DM, or no treatment administered 30 minutes prior to bedtime.

Main Outcome Measures: Cough frequency, cough severity, bothersome nature of cough, and child and parent sleep quality.

Results: Significant differences in symptom improvement were detected between treatment groups, with honey consistently scoring the best and no treatment scoring the worst. In paired comparisons, honey was significantly superior to no treatment for cough frequency and the combined score, but DM was not better than no treatment for any outcome. Comparison of honey with DM revealed no significant differences.

Conclusions: In a comparison of honey, DM, and no treatment, parents rated honey most favorably for symptomatic relief of their child's nocturnal cough and sleep difficulty due to upper respiratory tract infection. Honey may be a preferable treatment for the cough and sleep difficulty associated with childhood upper respiratory tract infection.

Trial Registration: clinicaltrials.gov Identifier: NCT00127686.

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COUGH IS THE REASON FOR nearly 3% of all outpatient visits in the United States, more than any other symptom, and it most commonly occurs in conjunction with an upper respiratory tract infection (URI).[1] At night, it is particularly bothersome because it disrupts

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sleep. Despite the common occurrence of URIs and cough, there are no accepted therapies for this annoying symptom. The use of dextromethorphan (DM), the most common over-the-counter (OTC) antitussive, for treatment of cough in childhood is not supported by the American Academy of Pediatrics or the American College of Chest Physicians.[2,3] Nonetheless, consumers spend billions of dollars per year on OTC medications for cough.[4,5]

We have previously shown that neither DM nor diphenhydramine was superior to placebo for outcomes related to cough and sleep quality when rated subjectively by parents.[6] In that study, the medications failed to produce an improvement in the frequency, severity, or bothersome nature of the cough to a greater degree than placebo. Importantly for parents, neither their child's sleep nor their own sleep was significantly better when their child received medication compared with placebo.

In many cultures, alternative remedies such as honey are used to treat URI symptoms including cough.[7] In contrast to DM, however, honey is generally believed to be safe outside of the infant population. Honey has many purported health benefits and has repeatedly been shown to aid in wound healing, even for children.[8-11] For cough and cold symptoms,

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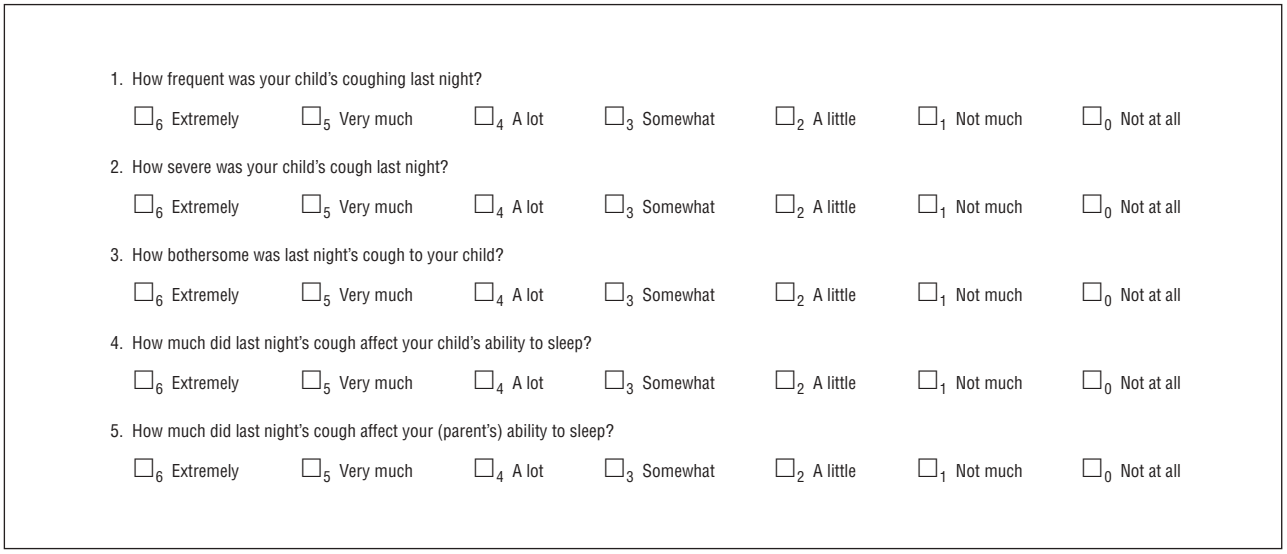

Figure 1. Survey questions to assess nocturnal cough and sleep difficulty.

honey is cited by the World Health Organization as a potential treatment.[12] In the World Health Organization report on the treatment of URIs in young children, honey is considered as a demulcent that is cheap, popular, and safe. Although there is no scientific evidence to support the use of honey for symptoms associated with a URI, it is suggested in the World Health Organization report that demulcents may soothe the throat and can be recommended to provide some relief from cough in children. In addition to the demulcent effect, honey has antioxidant properties and increases cytokine release, which may explain its antimicrobial effects.[13-17]

The objective of this trial was to compare the effects of a single nocturnal dose of honey or honey-flavored DM with no treatment on nocturnal cough and the sleep difficulty associated with URIs. A no-treatment arm was included instead of one with a placebo group for 2 reasons: (1) our previous study found no difference between DM and placebo for any outcome,[6] so including both a DM arm and a placebo arm would be unnecessary, and (2) a critique suggested that the study cohort was already improving at the time when DM or placebo was given, which limited our ability to detect a treatment effect.[18] Given the previous demonstration of DM's nonsuperiority to placebo, this study design allowed us to address previous critiques and answer a clinically important question by hypothesizing that both honey and DM will be superior to no treatment for control of nocturnal cough due to URI as well as its associated sleep difficulty.

METHODS

From September 2005 through March 2006, patients were recruited from a single university-affiliated pediatric practice in Hershey, Pennsylvania, on presentation for an acute care visit. Eligible patients were aged 2 through 18 years with cough attributed to URIs. The URIs were characterized by the presence of rhinorrhea and cough for 7 or fewer days' duration. Other symptoms may have included but were not limited to congestion, fever, sore throat, myalgias, and headache. Patients were excluded if they had signs or symptoms of a more treatable disease (eg, asthma, pneumonia, laryngotracheobronchitis, sinusitis, allergic rhinitis). They were also ineligible when they had a history of reactive airways disease, asthma, or chronic lung disease or were using a drug known to inhibit the metabolism of DM, such as selective serotonin reuptake inhibitors. Subjects were also excluded if on the prior evening they had taken a medication that included an antihistamine or DM hydrobromide within 6 hours of bedtime or DM polistirex within 12 hours of bedtime on the evening prior to or on the day of enrollment. Patients were not excluded when analgesic medications such as acetaminophen or ibuprofen were administered on either night of the study. While many more patients with URIs presented to the practice during the recruitment period, the exclusions, particularly the exclusion of taking medication on the previous evening, disqualified many subjects.

Subjective parental assessments of their child's cough and sleep difficulty on the previous night were assessed after informed consent was obtained through previously validated questions using a 7-point Likert scale (**Figure 1**).[19] Trained study coordinators were responsible for survey administration, and survey responses ranged from extremely (6 points) to not at all (0 points). In an effort to study a population that was likely to receive a therapeutic intervention by parents, minimum symptom severity criteria for enrollment were established. Only parents who answered at least somewhat (3 points) for a minimum of 2 of the 3 questions related to nocturnal cough frequency, effect on the child's sleep, and effect on parental sleep based on the previous night's symptoms were eligible.

After stratification for age (ages 2-5, 6-11, and 12-18 years), each child was randomly assigned in a partially double-blinded fashion to receive artificially honey-flavored DM (17 mg/5 mL prepared using DM hydrobromide powder [100% pure United States Pharmacopeia grade], artificial honey flavoring, coloring, stevia liquid extract, methocel, and simple syrup [Professional Compounding Centers of America, Houston, Texas]), buckwheat honey, or nothing in a 10-mL syringe. A compounding pharmacy prepared the DM to approximate the consistency, texture, flavor, smell, and sweetness of honey. The randomization sequence was constructed by a statistician not affiliated with the study (Susan Boehmer, MS) and was then used by the study coordinators to assign treatment groups.

The syringes used for all of the 3 treatment groups were opaque and were placed in brown paper bags to avoid investigator unblinding. Although the no-treatment group was not

Table. Baseline Characteristics[a]

Characteristic	Patients Receiving Honey (n=35)	Patients Receiving DM (n=33)	Patients Receiving No Treatment (n=37)
Age, median±interquartile range, y	5.43±3.81	4.42±3.83	5.22±4.33
Sex, No. (%)			
Female	15 (43)	19 (58)	22 (59)
Male	20 (57)	14 (42)	15 (41)
Duration of illness, mean±SD, d	5.00±1.69	4.21±1.63	4.70±1.66
Cough frequency score, mean±SD	4.00±0.91	3.76±1.12	3.73±0.93
Cough severity score, mean±SD	4.00±0.97	3.94±1.12	3.97±1.09
Cough bothersome score, mean±SD	4.03±1.18	4.12±1.05	3.86±1.06
Cough effect on child sleep score, mean±SD	3.91±1.04	3.73±1.31	3.97±1.04
Cough effect on parent sleep score, mean±SD	4.00±1.43	4.00±1.37	3.65±1.38
Combined symptom score, mean±SD	19.94±4.39	19.55±4.18	19.19±3.89

Abbreviation: DM, dextromethorphan.
[a]No significant difference between treatment groups exists for any baseline characteristic.

blinded to their treatment arm, the honey and DM groups remained blinded. Dosage for DM approximated typical OTC label recommendations, with children aged 2 to 5 years receiving 8.5 mg/dose (1/2 teaspoon), children aged 6 to 11 years receiving 17 mg/dose (1 teaspoon), and children aged 12 to 18 years receiving 34 mg/dose (2 teaspoons). Of note, these concentrations slightly exceed typical OTC products, which contain 15 mg/5 mL, and were the result of the compounding process but may be more likely to achieve a beneficial effect based on our previous analyses.[20] For the honey group, the volume of honey dispensed was equivalent to the age-driven volume dispensed for DM. The bags and syringes were refrigerated prior to being dispensed. Parents were instructed that their child's treatment could be given with a noncaffeinated beverage and should be administered within 30 minutes of the child going to sleep. A second survey asking the same questions as those answered at enrollment was then administered via telephone interview the following day to the same parent by trained study coordinators (J.B., A.M., Sarah Sturgis, CRNP, Jennifer Stokes, RN, Susan LaTournous, RN, and Diane Kitch, RN), who were blinded to the treatment group, to assess symptom severity for the night when DM, honey, or no treatment was given. No physician examination was performed on the second study day unless dictated by illness progression.

The prospectively estimated sample size necessary to detect a 1-point difference between any 2 treatment groups with 80% power was 35 subjects per treatment group for a total sample size of 105 subjects with $\alpha = .05$. This calculation was based on a 2-sided, 2-sample t test inflated to reflect the loss of efficiency that would result if it was necessary to use Wilcoxon-Mann-Whitney tests for pairwise comparisons of the treatments. The 1-point difference for the primary outcome has been used previously,[6] and it resulted in a sample size that is greater than several other well-known and similar clinical trials.[21,22] The principal outcome measure of interest was the change in the frequency of cough between the 2 nights, and secondary outcome measures of importance were changes in the cough severity, the bothersome nature of the cough, the effect of the cough on sleep for both the child and parents, and the combined score of these 5 measures.

Baseline characteristics were compared between treatment groups using a χ^2 test for sex, a Kruskal-Wallis test for age, and 1-way analysis of variance for the remaining variables. The cough outcomes showed no significant departures from normality; therefore, treatment group comparisons were conducted using 1-way analysis of variance. The Tukey method was used to adjust P values for the pairwise treatment comparisons for each cough outcome. These analyses were extended to include age (in continuous form) and sex separately in analysis of covariance models. As adjustment for these covariates did not change the findings, the results of the unadjusted analyses are reported. Fisher exact tests were used to compare adverse event rates between treatments.

The study was approved by the Pennsylvania State University College of Medicine's Human Subjects Protection Office, and the trial was registered at http://www.clinicaltrials.gov prior to the first subject's enrollment. Informed consent was obtained from all of the participating parents and verbal assent was obtained from all of the children aged 7 years or older.

RESULTS

One hundred thirty children with URIs were enrolled and 105 (81%) completed the single-night study. The median age of the patients completing the study was 5.22 years (range, 2.22-16.92 years), with no significant difference between treatment groups (**Table**). Thirty-five patients received honey, 33 received DM, and 37 received no treatment. Fifty-three percent of the children were female and the participants were ill a mean±SD of 4.64±1.68 days before participation, without significant differences in either variable between treatment groups ($P = .60$). In addition, there were no significant differences between measures of symptom severity at baseline.

Symptom scores were obtained to describe the night before enrollment when no participants received treatment, and they were compared with scores from the subsequent night when honey, honey-flavored DM, or no treatment was given before bed. When separated by treatment group, significant differences were detected in the amount of improvement reported for all of the study outcomes in the planned 3-way comparison (**Figure 2**). All of the outcomes found honey to yield the greatest improvement, followed by DM, while no treatment consistently showed the least amount of improvement. For cough frequency, those who received honey had a mean 1.89-point improvement as rated by their parents compared with a 1.39-point change for those receiving DM and a 0.92-point change for those who had no treatment on the second night ($P < .001$). Parents also noted

similar improvements in the severity of their child's cough: 1.80 points with honey, 1.30 points with DM, and 1.11 points with no treatment ($P<.001$). While parents felt the cough also was less bothersome on the second night, again honey provided the greatest relief with a 2.23-point change compared with a 1.94-point change and a 1.30-point change for those children who received DM and no treatment, respectively ($P<.001$). Parents rated their children's sleep better after receiving honey, with a 2.49-point improvement for the honey group compared with a 1.79-point change for the DM group and a 1.57-point change for those not receiving treatment on the second night ($P<.001$). As might be expected, parental sleep improved in a fashion similar to that of their children, with the honey treatment arm improving the most by a mean of 2.31 points, followed by 1.97 points for DM and 1.51 points for no treatment ($P<.001$). When the results for these outcomes were combined by adding the scores from the individual categories, honey again proved to be the most effective treatment. The children in this group improved by an average of 10.71 points compared with 8.39 points for DM-treated children and 6.41 points for those who were not treated ($P<.001$).

In pairwise comparisons, honey was significantly superior to no treatment for our a priori primary outcome of cough frequency ($P=.01$) as well as the combined symptom score ($P=.04$), with marginally significant superiority for child sleep ($P=.09$) and the bothersome nature of the cough ($P=.08$). Nonsignificant outcomes included cough severity ($P=.18$) and parent sleep ($P=.17$). In contrast, DM was not significantly better than no treatment for any study outcome. Similarly, pairwise comparison of honey with DM revealed no statistically significant differences.

Even though the mean illness duration was not significantly different between treatment groups ($P=.15$), because of the possibility that the treatment effect was modified by the duration of illness, the analysis of variance models were extended to include the duration of illness and an interaction term between treatment and the duration of illness. This interaction term only reached statistical significance for cough frequency ($P=.05$) and child's sleep ($P=.04$); however, all of the outcome measures showed a similar pattern of treatment effect modification. Improvement with the use of honey or no treatment increased as the duration of illness increased, whereas improvement with DM decreased as the duration of illness increased.

Few adverse events occurred in this investigation. The combination of mild reactions that include hyperactivity, nervousness, and insomnia occurred in 5 patients treated with honey, 2 patients in the DM group, and no patients in the no-treatment arm ($P=.04$). In the honey group, the parent of 1 patient reported drowsiness and the parents of 2 patients reported stomachache, nausea, or vomiting, but these adverse events were not significant when examined separately from a statistical perspective (drowsiness, $P=.65$; stomachache, nausea, vomiting, $P=.21$).

COMMENT

The results of this study demonstrate that in the overall comparison of the 3 treatment groups, honey was the most effective treatment for all of the outcomes related to cough, child sleep, and parent sleep. Further, honey but not DM was superior to no treatment for nocturnal symptoms associated with childhood URI. Notably, however, direct comparison between honey and DM yielded no statistically significant differences. These findings complement the results of our previous study[6] that found no difference between DM, diphenhydramine, or placebo for children with URIs, and they now provide a generally safe and well-tolerated alternative for practitioners to recommend.

Honey has well-established antioxidant and antimicrobial effects,[13,15,23-30] which have been suggested as the mechanism for its efficacy in wound healing and may help to explain its superiority in this study. Buckwheat honey is a dark variety of honey, and darker honeys tend to have a higher content of phenolic compounds. These compounds have been associated with the antioxidant properties of honey that may have contributed to its effect in this study.[15,16,31] Further, its topical demulcent effect may contribute to its benefits for cough as postulated by the World Health Organization review.[12]

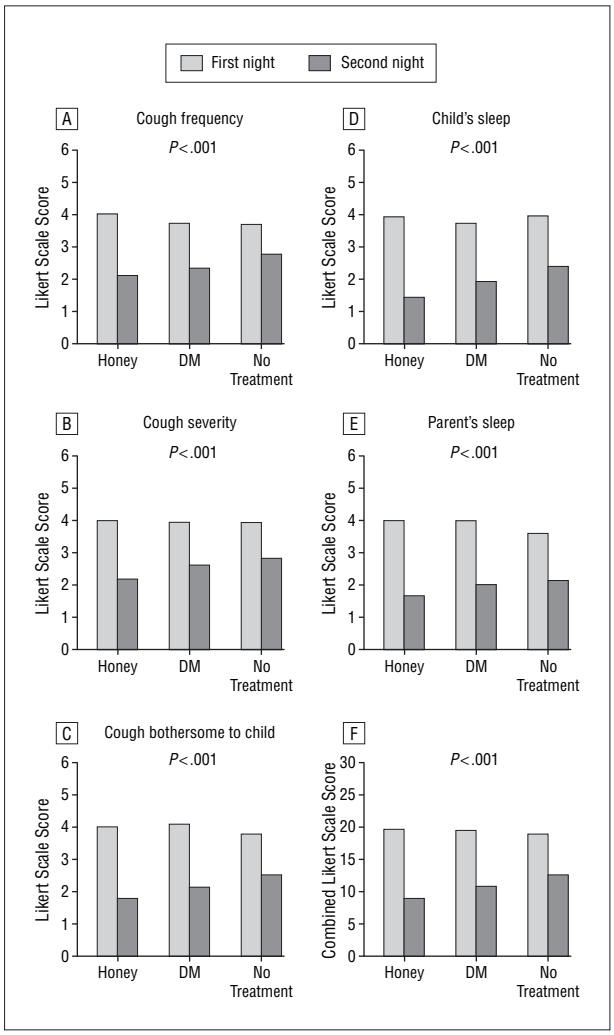

Figure 2. Comparison of the effect of honey, dextromethorphan (DM), and no treatment on cough frequency (A), cough severity (B), the cough being bothersome to the child (C), the child's sleep (D), the parent's sleep (E), and the combined symptom score (F).

Another explanation for some of the beneficial effects of honey was recently described in a provocative review by Eccles.[32] This article argues that the sweetness of liquid preparations used to treat cough accounts for a significant portion of the treatment effect and also explains why studies have shown that antitussive preparations containing DM are not significantly superior to sweet, liquid placebos. This hypothesis is based on the suggestion that sweet substances naturally cause reflex salivation and may also cause the secretion of airway mucus and lead to a demulcent effect on the pharynx and larynx, thereby reducing cough (particularly dry, unproductive cough). For productive cough, Eccles suggests that these secretions could improve mucociliary clearance in the airway via an expectorant mechanism. Additionally, the review mentions the evidence related to endogenous opioids that are produced following consumption of sweet substances, a phenomenon that has been repeatedly studied for its analgesic properties. Because of the close anatomical relationship between the sensory nerve fibers that initiate cough and the gustatory nerve fibers that taste sweetness, Eccles suggests that an interaction between the opioid-responsive sensory fibers and the gustatory nerves may help to produce the antitussive effects of sweet substances via a central nervous system mechanism.

Dextromethorphan continues to be used very frequently in the United States despite numerous studies, evidence-based reviews, and policy statements describing its lack of efficacy.[2,3,6,21,22,33-38] Although it was generally well tolerated in the cohort of children who took the medication in this study, its OTC availability is especially concerning given the numerous reports of serious adverse events described in the medical literature, such as dystonia,[39] anaphylaxis,[40] and bullous mastocytosis[41] with standard doses, and dependence,[42,43] psychosis,[44,45] mania,[46,47] hallucinations,[48] ataxia,[49,50] somnolence,[50] insulin-dependent diabetes mellitus,[51] peripheral neuropathy,[52] cerebellar degeneration,[53] megaloblastic anemia,[52,53] and death[54] with higher doses. Further, DM is increasingly being used as a recreational drug of abuse, particularly by adolescents,[55-64] and one recent report[63] indicated that nearly 5% of 12th graders in Dayton, Ohio, have tried this drug for this purpose.

In contrast with DM, honey is generally recognized as safe with the exceptions of the risk of infantile botulism for children younger than 1 year[65-68] and the rare risk of grayanotoxin-mediated syndrome characterized by salivation, emesis, circumoral and extremity paresthesias, hypotension, bradycardia, and, occasionally, cardiac rhythm disturbances.[69] Our study did find that the mild adverse effect grouping of hyperactivity, nervousness, and insomnia was significantly more common in those treated with honey, a finding that could affect clinician recommendations.

The use of a no-treatment arm somewhat negates the criticism of our prior study that argued that the effect of DM could not be determined because of the large placebo effect seen. The current results surprisingly indicate that DM was not significantly better than no treatment at all. While the trend seen in the results suggests that a larger sample size may have had enough statistical power to detect a difference between DM and no treatment, for the individual outcome measures, the observed differences were all smaller than the 1-point difference believed to be clinically meaningful prior to study initiation. In any case, the fact that there was sufficient power to find that honey was superior to no treatment adds to the validity of our previous findings suggesting that DM was no better than a placebo treatment of simple syrup without a pharmacologically active substance.

This study is somewhat limited by the fact that each child had a physician visit between the 2 nights of the study, which may provide some of the explanation for the improvement in all of the groups, including the no-treatment group. Alternatively, much of the improvement can also be attributed to the natural history of URIs, which generally improve with time and supportive care. The subjective survey used for this study may also be considered by some to be a limitation, but clinicians and parents often make decisions based on subjective assessment of symptom severity as has been argued previously.[22,70] Additionally, investigators at the Massachusetts General Hospital recently validated this survey with 120 caregivers of children aged 1 to 18 years and found it to be reliable for assessing changes in cough frequency and severity over time.[19] Further, compliance with medication administration could not be guaranteed even though every parent did report that the treatment was taken by their child without difficulty regardless of randomization arm, but the lack of treatment in 1 of the study arms could be viewed as causing biased results in that treatment arm.

As we have stated previously, the desire to ease the symptoms associated with URIs, particularly cough and its associated sleep difficulty, is great.[6] Both physicians and parents want symptomatic relief for children afflicted with these common and annoying illnesses. While our findings and the absence of contemporary studies supporting the use of DM continue to question its effectiveness for the treatment of cough associated with URIs, we have now provided evidence supporting honey, which is generally regarded as safe for children older than 1 year, as an alternative. While additional studies to confirm our findings should be encouraged, each clinician should consider the findings for honey, the absence of such published findings for DM, and the potential for adverse effects and cumulative costs associated with the use of DM when recommending treatments for families.

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Author Contributions: Dr Paul takes responsibility for the integrity of the data. Dr Shaffer had full access to all of the data in the study and takes responsibility for the accuracy of the data analysis. *Study concept and design:* Paul, Beiler, and Berlin. *Acquisition of data:* Beiler, McMonagle, and Duda. *Analysis and interpretation of data:*

Paul, Beiler, Shaffer, Duda, and Berlin. *Drafting of the manuscript:* Paul. *Critical revision of the manuscript for important intellectual content:* Beiler, McMonagle, Shaffer, Duda, and Berlin. *Statistical analysis:* Shaffer. *Obtained funding:* Paul. *Administrative, technical, and material support:* Paul, Beiler, McMonagle, and Duda. *Study supervision:* Paul, Beiler, Duda, and Berlin.

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