Original Investigation

Placebo Effect in the Treatment of Acute Cough in Infants and Toddlers
A Randomized Clinical Trial

Ian M. Paul, MD, MSc; Jessica S. Beiler, MPH; Julie R. Vallati, LPN; Laura M. Duda, MD; Tonya S. King, PhD

IMPORTANCE Cough is one of the most common reasons why children visit a health care professional.

OBJECTIVES To compare the effect of a novel formulation of pasteurized agave nectar vs placebo and no treatment on nocturnal cough and the sleep difficulty associated with nonspecific acute cough in infants and toddlers.

DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial performed in 2 university-affiliated outpatient, general pediatric practices from January 28, 2013, through February 28, 2014, children 2 to 47 months old with nonspecific acute cough duration of 7 days or less were studied. Surveys were administered to parents on 2 consecutive days, the day of presentation (when no medication had been given the prior evening) and the next day (when agave nectar, placebo, or no treatment had been administered to their child before bedtime) according to a partially double-blind randomization scheme.

INTERVENTIONS A single dose of agave nectar, placebo, or no treatment administered 30 minutes before bedtime.

MAIN OUTCOMES AND MEASURES Cough frequency, cough severity, cough bothersomeness, congestion severity, rhinorrhea severity, and cough effect on child and parent sleep.

RESULTS Significant differences in symptom improvement were detected between the study groups ($P < .05$ for all, except $P = .06$ for cough bothersomeness), with agave nectar and placebo proving to be superior to no treatment, but no significant differences for any outcome were found when comparing agave nectar against placebo.

CONCLUSIONS AND RELEVANCE In a comparison of agave nectar, placebo, and no treatment, a placebo effect was demonstrated, with no additional benefit offered by agave nectar. Health care professionals should consider the potential benefits and costs when recommending a treatment with only a placebo effect for infants and toddlers with nonspecific acute cough.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01721395

Editorial page 1091

Journal Club Slides at jamapediatrics.com

CME Quiz at jamanetworkcme.com and CME Questions page 1164

Author Affiliations: Department of Pediatrics, Penn State College of Medicine, Hershey, Pennsylvania (Paul, Beiler, Vallati, Duda); Department of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania (Paul, King).

Corresponding Author: Ian M. Paul, MD, MSc, Department of Pediatrics, Penn State College of Medicine, Mail Code HS83, 500 University Dr, Hershey, PA 17033-0850 (ipaul@psu.edu).

JAMA Pediatr. 2014;168(12):1107-1113. doi:10.1001/jamapediatrics.2014.1609
Published online October 27, 2014.

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Tunisia Johnson on 06/14/2023

KINDERFARMS Ex. 1043
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

Cough is a frequent symptom in infants and toddlers and is one of the most common reasons why children visit a health care professional.[1] It is particularly bothersome at night, as evidenced by a recent study[2] of the effect of cough on sleep for infants with colds, which found that cough disturbed the sleep of 88% of the children and 72% of their parents.

For such a common and bothersome symptom, the desire for effective therapies is high, but little evidence supports the use of over-the-counter medicines for acute cough, particularly in younger children.[3,4] Moreover, the US Food and Drug Administration has issued a warning that over-the-counter cough and cold medicines, including antihistamines, decongestants, antitussives, and expectorants, should not be administered to children younger than 2 years owing to safety concerns and the lack of proven efficacy.[5]

An alternative to pharmaceutical products for the treatment of cough is honey, a food used by many cultures around the world to relieve cough.[6] A randomized study[7] of the effect of a single dose of buckwheat honey, honey-flavored dextromethrophan, or no treatment administered 30 minutes before bedtime found that parents rated honey most favorably for symptomatic relief of their child's nocturnal cough and the sleep difficulty due to upper respiratory tract infection. Similar results indicating the effectiveness of honey were discovered in 2 other trials.[8,9] Unfortunately, children younger than 1 year are precluded from consuming honey owing to concerns of *Clostridium botulinum* spores found in it that can lead to infant botulism.[10]

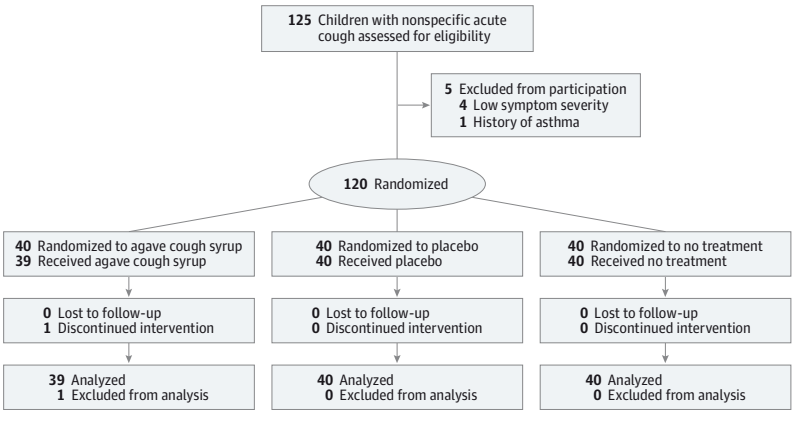
The consumption of agave nectar, a product with properties similar to those of honey, has not been associated with botulism to our knowledge, but no studies to date have evaluated its use for nocturnal cough. We hypothesized that the demulcent effect and sweet taste of agave nectar would provide relief for cough in children similar to that of honey. As such, we compared the effect of a novel formulation of pasteurized agave nectar vs placebo and no treatment on nocturnal cough and the sleep difficulty associated with nonspecific acute cough in infants and toddlers, a group with high need for therapy but few available means of symptom relief.

Methods

The study was approved by the Penn State College of Medicine Human Subjects Protection Office and was registered at http://www.clinicaltrials.govbefore enrollment of the first participant. From January 28, 2013, through February 28, 2014, patients were recruited from 2 university-affiliated outpatient, general pediatric practices in Hershey and Elizabethtown, Pennsylvania. Eligible patients were 2 to 47 months old with nonspecific acute cough duration of 7 days or less. Other symptoms may have included fever, congestion, and rhinorrhea, as well as other common comorbid findings. Patients were excluded if they had signs or symptoms of a more treatable disease (eg, asthma, pneumonia, or laryngotracheobronchitis). They were also ineligible if they had a history of asthma, chronic lung disease, or other severe chronic diseases. Those with allergies to agave nectar or grape flavoring were excluded. Finally, patients were excluded if they had used any medication or honey to treat cough within 6 hours of bedtime on the evening before or on the day of enrollment.

After written informed consent was obtained, each child was randomized in a partially double-blind scheme to one of the following 3 study groups: (1) pasteurized agave nectar (with natural grape flavoring, citric acid, sodium citrate, and potassium sorbate) from Zarbee's Inc, (2) natural grape-flavored water with caramel color (placebo), and (3) no treatment (**Figure 1**). For the 2 study groups receiving a study treatment, the dose volume distributed was stratified by age, with 3 mL for ages 2 to 5 months, 4 mL for ages 6 to 23 months, and 5 mL for ages 24 to 47 months. The randomization sequence was constructed by a statistician not affiliated with the study and was used to assign study groups stratified by age category with mixed block sizes. All study parents were instructed on routine care for children with nonspecific acute cough, including hydration measures, saline nasal spray use, and the use of acetaminophen or ibuprofen (for ages ≥6 months) as needed for comfort. Parents were asked not to give honey or any ex-

Figure 1. Study CONSORT Diagram



Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Tunisia Johnson on 06/14/2023

KINDERFARMS Ex. 1043
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

cluded cold, allergy, or sinus over-the-counter medications, including topical vapor rubs or similar compounds administered via humidifiers, to their child at any time after enrollment. They were also instructed to avoid giving caffeinated beverages to their child within 4 hours of bedtime. Subjective parent assessments of their child's symptoms on the previous night were recorded with a modified version of a validated questionnaire[11] using a 7-point ordinal scale (**Figure 2**). Trained study coordinators (including J.R.V.) were responsible for survey administration, and survey responses ranged from the most severe symptoms (7 points) to no symptoms (1 point). Minimum symptom severity criteria for enrollment were established. Only parents answering at least "moderately often" or "moderately severe" on at least 2 of 3 questions related to cough frequency, cough effect on child sleep, and cough effect on parent sleep based on the previous night's symptoms were eligible.

To maintain investigator blinding, all study group participants received an opaque paper bag containing an opaque syringe filled with agave nectar, placebo, or no treatment. Thirty minutes before their child retired for the evening, parents opened their opaque bag and removed the syringe. Following this, for the agave nectar and placebo groups, parents were instructed to administer the entire contents of the syringe to their child.

A second survey, asking the same questions related to the child's illness as those answered at enrollment, was completed by parents within 30 minutes of waking the morning following the above procedures. Questions were included to assess additional treatments, including analgesics and saline nasal spray use. Specific questions were asked about adverse effects such as hyperactivity, sleepiness, headache, and rash. Finally, parents were asked what treatment they thought their child had received. Blinded study coordinators contacted parents during that day to retrieve responses. A physician examination was not routinely performed on the second study day.

Sample size calculations indicated that 120 participants (40 per study arm) would have 80% power to detect a 0.5-point difference between the study groups incrementally for the primary efficacy measure of change in cough frequency between the first night and the end of the second night. This calculation assumed $\alpha = .05$ and an SD estimated at 1.35. The sample size estimate included a 5% withdrawal or loss to follow-up rate. In addition, this sample size provided 88% power to evaluate a test of trend among the 3 study groups within the analysis of variance framework.

Baseline and demographic features were compared among study groups using χ^2 test and Fisher exact test where appropriate for sex and race/ethnicity and *F* test for weight and age. Within-group comparisons for the 2 nights were conducted using paired *t* test. Between-group comparisons were conducted by analysis of covariance, which was deemed appropriate after assessment of the outcome variable distribution. For the primary analysis of treatment effect, the outcome of between-night change included baseline scores as a covariate. Following a hierarchical analysis plan, if the overall comparison among the 3 study groups (2 *df*) was significant at $P < .05$, then pairwise comparisons across the 3 groups were performed. Fisher exact test was used to compare adverse reaction rates between treatments.

Figure 2. Survey Questions to Assess Nocturnal Upper Respiratory Infection Symptoms

1. How OFTEN did your child COUGH last night?

☐1	☐2	☐3	☐4	☐5	☐6	☐7
Not at all			Moderately often			Very often

2. How SEVERE was your child's COUGH last night?

☐1	☐2	☐3	☐4	☐5	☐6	☐7
Not at all			Moderately severe			Very severe

3. How BOTHERSOME was your child's COUGH last night?

☐1	☐2	☐3	☐4	☐5	☐6	☐7
Not at all			Moderately severe			Very severe

4. How SEVERE was your child's STUFFY NOSE last night?

☐1	☐2	☐3	☐4	☐5	☐6	☐7
Not at all			Moderately severe			Very severe

5. How SEVERE was your child's RUNNY NOSE last night?

☐1	☐2	☐3	☐4	☐5	☐6	☐7
Not at all			Moderately severe			Very severe

6. How much did last night's cough affect your CHILD'S ABILITY TO SLEEP?

☐1	☐2	☐3	☐4	☐5	☐6	☐7
Not at all			A moderate amount			Very much

7. How much did your child's cough affect YOUR OWN ABILITY TO SLEEP last night?

☐1	☐2	☐3	☐4	☐5	☐6	☐7
Not at all			A moderate amount			Very much

Results

One hundred twenty-five children with nonspecific acute cough were enrolled, and 119 (95.2%) completed the single-night study. The mean (SD) age of the children completing the study was 22.9 (14.0) months (**Table**). Fifty percent of these participants were female, and 86.6% were described by their parents as being of white race/ethnicity and non-Hispanic. The cohort had been coughing a mean (SD) of 4.0 (1.5) days before enrollment. Thirty-nine children completing the study were randomized to the agave nectar group, while 40 children were randomized to each of the other study groups. No demographic or baseline symptom severity differences were observed between the study groups.

The baseline symptom scores describing the night before enrollment (when no participants received treatment) were compared with scores from the subsequent night (when agave nectar, placebo, or no treatment was given before bedtime), and within each study group all outcomes were significantly improved on the subsequent night ($P < .05$ for all). When separated by study group, significant differences were detected in the amount of improvement reported for all study outcomes except for cough bothersomeness to the child in the planned 3-way comparison (**Figure 3**).

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Tunisia Johnson on 06/14/2023

KINDERFARMS Ex. 1043
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

Page 3 of 7

Table. Baseline Characteristics Among 119 Study Group Participants[a]

Characteristic	Agave Nectar (n = 39)	Placebo (n = 40)	No Treatment (n = 40)
Age, mean (SD), mo	23 (15)	24 (14)	22 (13)
Sex, No. (%)			
Female	16 (41.0)	24 (60.0)	20 (50.0)
Male	23 (59.0)	16 (40.0)	20 (50.0)
Race/ethnicity, No. (%)			
White	34 (87.2)	32 (80.0)	37 (92.5)
Black	2 (5.1)	2 (5.0)	1 (2.5)
Hispanic	2 (5.1)	3 (7.5)	1 (2.5)
Asian	1 (2.6)	0	0
>1 Race/ethnicity	0	2 (5.0)	1 (2.5)
Other	0	1 (2.5)	0
Duration of cough, mean (SD), d	4.1 (1.6)	4.2 (1.5)	3.8 (1.5)
Symptom score, mean (SD)			
Cough frequency	5.2 (1.2)	5.6 (1.3)	5.2 (1.3)
Cough severity	5.2 (1.4)	5.3 (1.3)	5.3 (1.3)
Cough bothersomeness	5.4 (1.3)	5.6 (1.4)	5.5 (1.3)
Congestion severity	5.0 (1.8)	5.5 (1.4)	5.0 (1.6)
Rhinorrhea severity	5.3 (1.7)	5.1 (1.5)	4.8 (1.7)
Cough effect on child sleep	5.4 (1.3)	5.6 (1.5)	5.7 (1.4)
Cough effect on parent sleep	5.6 (1.3)	5.7 (1.5)	5.8 (1.3)
Combined symptom	37.1 (7.1)	38.4 (7.4)	37.3 (6.6)

[a] No significant difference between the study groups was observed for any baseline characteristic.

Because differences existed for all outcomes except one, pairwise comparisons were then performed. For all outcomes except for cough bothersomeness to the child, the agave nectar and placebo groups had significant improvement compared with the no treatment group, but no differences were detected for any outcome between the agave nectar and placebo groups.

A combined symptom score was calculated using all study outcomes, including cough frequency, cough severity, congestion severity, rhinorrhea severity, and cough effect on child and parent sleep. Again, agave nectar and placebo were superior to no treatment, but no significant differences were detected between the agave nectar and placebo groups.

To help understand parent ability to judge their child's nocturnal symptoms, parents quantified the number of times they checked on their child between the time the child went to sleep and the time he or she awoke. On the night before enrollment, parents reported checking their child a median of 4 (interquartile range, 2.5-5) times; they also checked their child a median of 4 (interquartile range, 2-4) times on the treatment night. No significant difference was detected between the study groups for either night.

Several secondary analyses were conducted. First, no effect of illness duration was observed on treatment effect. Next, parents were asked about other therapies used on the treatment night before and after the treatment bag was opened, with no significant differences between the study groups found for any remedy.

Given that honey is not recommended for children younger than 1 year, a subgroup analysis was performed for the 30 children in this age category. For all outcomes, agave nectar resulted in more than a 0.5-point greater improvement compared with placebo (the a priori definition of a clinically meaningful difference), a finding limited by the small subgroup sample size and the reduced power to detect a statistically significant finding. The symptom reductions between the first and second nights comparing agave nectar vs placebo among children younger than 1 year all showed greater improvement with agave nectar and were as follows: −2.5 vs −1.7 for cough frequency (difference, 0.8; 95% CI, −0.6 to 2.3), −2.6 vs −1.8 for cough severity (difference, 0.8; 95% CI, −0.7 to 2.2), −2.9 vs −1.8 for cough bothersomeness (difference, 1.1; 95% CI, −0.6 to 2.8), −1.6 vs −0.3 for congestion severity (difference, 1.3; 95% CI, 0.0-2.6), −2.3 vs −1.3 for rhinorrhea severity (difference, 1.0; 95% CI, −0.4 to 2.4), −3.3 vs −2.3 for cough effect on child sleep (difference, 1.0; 95% CI, −0.7 to 2.7), −3.4 vs −2.3 for cough effect on parent sleep (difference, 1.1; 95% CI, −0.7 to 2.8), and −19.0 vs −11.4 for the combined symptom score (difference, 7.6; 95% CI, −1.3 to 16.6).

Adverse effects were uncommon in the study, with 5 reported in the agave nectar group, 6 in the placebo group, and none in the no treatment group. No significant differences were observed between the study groups for any individual adverse event.

Seventy-seven percent (30 of 39) of agave nectar group parents and 47.5% (19 of 40) of placebo group parents guessed their child's study group correctly. Among the no treatment group, 4 parents erroneously answered placebo and 1 parent erroneously answered agave nectar when reporting their child's treatment the night before enrollment, with 87.5% (35 of 40) reporting their child's study arm correctly.

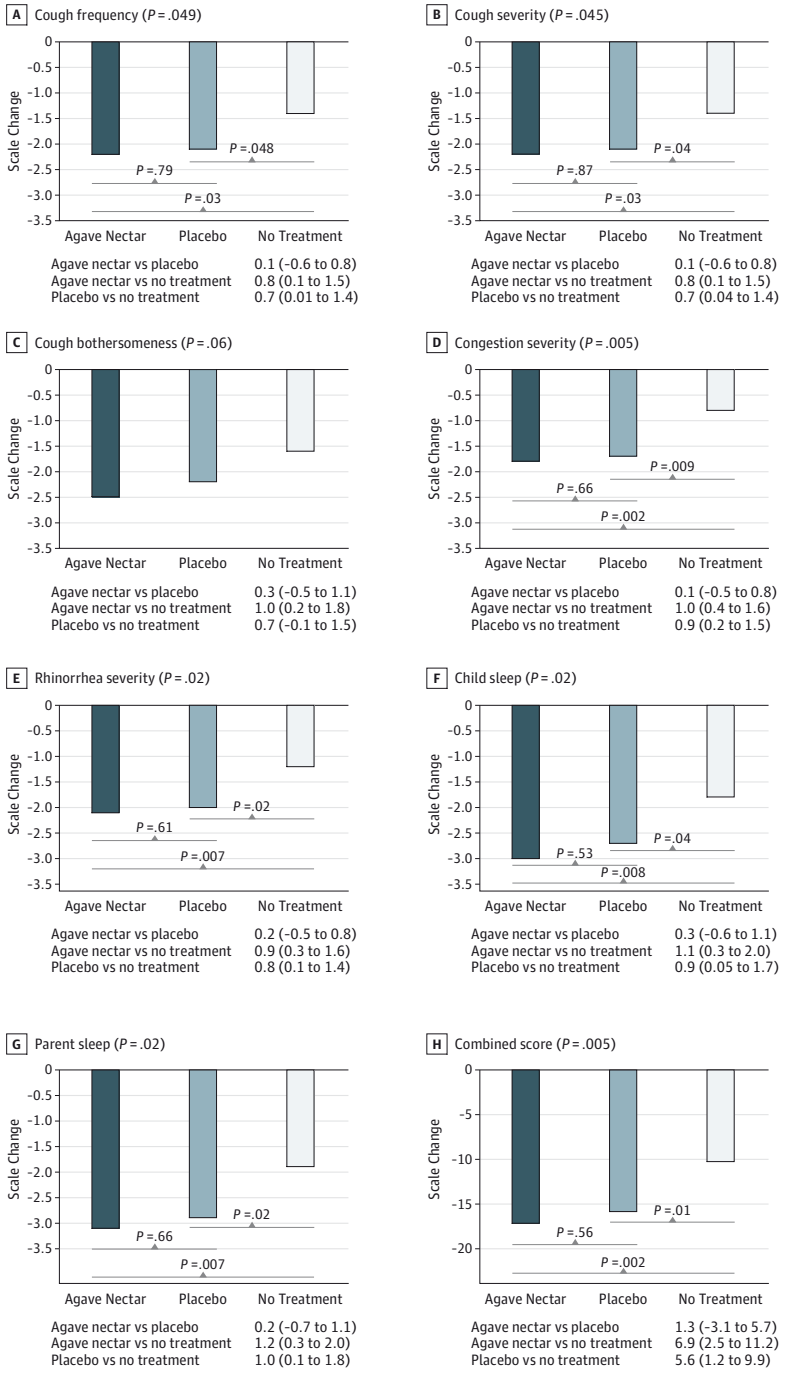
Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Tunisia Johnson on 06/14/2023

KINDERFARMS Ex. 1043
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

Page 4 of 7

Figure 3. Between-Night Treatment Effects of Agave Nectar, Placebo, and No Treatment on Study Outcomes Using a Likert-Type Scale



A, Cough frequency. B, Cough severity. C, Cough bothersomeness. D, Congestion severity. E, Rhinorrhea severity. F, Cough effect on child sleep. G, Cough effect on parent sleep. H, Combined symptom score. *P* values in figure parts represent 3-way treatment comparisons. Comparisons at the bottom of figure parts are between-group model-adjusted differences (95% CIs) in improvement.

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Tunisia Johnson on 06/14/2023

KINDERFARMS Ex. 1043
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

Discussion

This study highlights that a significant placebo effect exists in the treatment of young children with nonspecific acute cough because agave nectar and placebo both resulted in perceived improvement of child symptoms by parents compared with no treatment. While it is somewhat disappointing that agave nectar does not appear to offer added benefit over a placebo, these findings suggest that the common clinical advice of watchful waiting with no treatment may not be the best advice for parents whose infants and toddlers are struggling with cough and its associated sleep disruption.

Agave nectar was a promising choice to study as the base compound for an infant cough syrup given that it has sweetness, viscosity, and taste acceptability similar to honey, with the important lack of association with infant botulism. This sweet liquid is produced from the agave plant and has been shown to have anti-inflammatory properties,[12] although it lacks the antioxidant activity of honey.[13] However, placebo effects are common in pediatric clinical trials,[14] including studies[15-22] attempting to investigate treatments for cough and cold symptoms. Among studies of antitussive use in adults, Eccles[23] estimated that in 85% the treatment response can be attributed to a placebo effect, rendering the identification of pharmacologically beneficial remedies difficult. For infants and toddlers, providing relief may be even more difficult because anecdotal experience suggests that rhinorrhea and nasal congestion may be greater contributors to discomfort and sleep disruption than for older children and adults. Alternatively, the intriguing (although not statistically significant) findings among children younger than 1 year suggest that further evaluation among a larger cohort in this age group may be warranted. This group is the most germane to therapeutic measures for upper respiratory tract infection given that evidence-based therapies such as honey and topical vapor rubs containing camphor, menthol, and eucalyptus oils are not recommended for these children.[24,25]

The negative findings herein may actually strengthen the validity of 3 studies[7-9] demonstrating the beneficial effects of honey for children as young as 1 year. Each of those trials used almost identical methods as in the present study with agave nectar, but while the effects of agave nectar were indistinguishable from those of placebo, several varieties of honey were used in those trials, and each has shown added benefit beyond placebo.

This study is somewhat limited by the fact that each child had a physician visit between the 2 nights of the study, which may explain some of the improvement in all study groups, including the no treatment group. The finding that differences existed between the 2 active arms and the no treatment group suggests that parents receive some added level of reassurance by administering a potential remedy to their child. Alternatively, much of the improvement can also be attributed to the natural history of upper respiratory tract infections, 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 health care professionals and parents often make decisions based on subjective assessment of symptom severity, as has been shown previously.[15,17] Furthermore, the survey used in this study was shown to be valid and reliable in the longitudinal assessment of pediatric cough.[11] Another potential limitation is that compliance with medication administration could not be guaranteed, although every parent reported that the treatment was taken by their child without difficulty regardless of the randomization arm, but the lack of treatment in one of the study arms could be viewed as causing biased results in that treatment arm.

Conclusions

While the results of this study did not demonstrate that agave nectar was superior to placebo for the treatment of nonspecific acute cough, the desire to ease cold symptoms and its associated sleep disruption is great. Both physicians and parents want symptomatic relief for children with these common and annoying illnesses. The significant placebo effect found warrants consideration as health care providers and parents determine how best to manage the disruptive symptoms that occur in the setting of upper respiratory tract infections among young children. Placebo could offer some perceived benefit, although at a financial cost, while reducing inappropriate antibiotic prescribing.

ARTICLE INFORMATION

Accepted for Publication: July 11, 2014.

Published Online: October 27, 2014. doi:10.1001/jamapediatrics.2014.1609.

Author Contributions: Ms Beiler had full access to all the data in the study and takes responsibility for the integrity of the data. Dr King takes responsibility for the accuracy of the data analysis.
Study concept and design: Paul, Beiler, King.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Paul, King.
Critical revision of the manuscript for important intellectual content: Beiler, Vallati, Duda, King.
Statistical analysis: King.
Obtained funding: Paul.
Administrative, technical, or material support: Paul, Beiler, Vallati, Duda.
Study supervision: Paul, Vallati.

Conflict of Interest Disclosures: Dr Paul reported serving as a paid consultant to Zarbee's Inc in 2012; this consulting relationship was discontinued upon discussions of performing a clinical trial. Dr Paul's relationship was evaluated and supervised by the Penn State College of Medicine Conflict of Interest System Committee. No other disclosures were reported.

Funding/Support: This study was funded by an unrestricted grant to the Penn State College of Medicine by Zarbee's Inc.

Role of the Funder/Sponsor: The funding source had the opportunity to review and comment on the study protocol and manuscript before submission, although the investigators were not obligated to make changes based on these comments. The funding source had no role in the conduct of the study, collection, management, analysis, and interpretation of the data or in the preparation of the manuscript and the decision to submit the manuscript for publication.

REFERENCES

1. Berger H, Jarosch E, Madreiter H. Effect of Vaporub and petrolatum on frequency and amplitude of breathing in children with acute bronchitis. *J Int Med Res*. 1978;6(6):483-486.

2. De Blasio F, Dicpinigaitis PV, Rubin BK, De Danieli G, Lanata L, Zanasi A. An observational study on cough in children: epidemiology, impact on quality

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Tunisia Johnson on 06/14/2023

KINDERFARMS Ex. 1043
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

of sleep and treatment outcome. *Cough*. 2012;8(1):1. doi:10.1186/1745-9974-8-1.

3. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev*. 2012;8(8):CD001831. doi:10.1002/14651858.CD001831.pub4.

4. Paul IM. Therapeutic options for acute cough due to upper respiratory infections in children. *Lung*. 2012;190(1):41-44.

5. Jaffe GV, Grimshaw JJ. Benylin expectorant versus actifed expectorant in the treatment of acute cough. *Br J Clin Pract*. 1985;39(6):238-242.

6. Pfeiffer WF. A multicultural approach to the patient who has a common cold. *Pediatr Rev*. 2005;26(5):170-175.

7. Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM Jr. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. *Arch Pediatr Adolesc Med*. 2007;161(12):1140-1146.

8. Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A comparison of the effect of honey, dextromethorphan, and diphenhydramine on nightly cough and sleep quality in children and their parents. *J Altern Complement Med*. 2010;16(7):787-793.

9. Cohen HA, Rozen J, Kristal H, et al. Effect of honey on nocturnal cough and sleep quality: a double-blind, randomized, placebo-controlled study. *Pediatrics*. 2012;130(3):465-471.

10. Cox N, Hinkle R. Infant botulism. *Am Fam Physician*. 2002;65(7):1388-1392.

11. Hartnick CJ, Zurakowski D, Haver K. Validation of a pediatric cough questionnaire. *Ear Nose Throat J*. 2009;88(11):1213-1217.

12. Monterrosas-Brisson N, Ocampo ML, Jiménez-Ferrer E, et al. Anti-inflammatory activity of different agave plants and the compound cantalasaponin-1. *Molecules*. 2013;18(7):8136-8146.

13. Phillips KM, Carlsen MH, Blomhoff R. Total antioxidant content of alternatives to refined sugar. *J Am Diet Assoc*. 2009;109(1):64-71.

14. Weimer K, Gulewitsch MD, Schlarb AA, Schwille-Kiuntke J, Klosterhalfen S, Enck P. Placebo effects in children: a review. *Pediatr Res*. 2013;74(1):96-102.

15. Hutton N, Wilson MH, Mellits ED, et al. Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. *J Pediatr*. 1991;118(1):125-130.

16. Korppi M, Laurikainen K, Pietikäinen M, Silvasti M. Antitussives in the treatment of acute transient cough in children. *Acta Paediatr Scand*. 1991;80(10):969-971.

17. Taylor JA, Novack AH, Almquist JR, Rogers JE. Efficacy of cough suppressants in children. *J Pediatr*. 1993;122(5, pt 1):799-802.

18. Clemens CJ, Taylor JA, Almquist JR, Quinn HC, Mehta A, Naylor GS. Is an antihistamine-decongestant combination effective in temporarily relieving symptoms of the common cold in preschool children? *J Pediatr*. 1997;130(3):463-466.

19. Paul IM, Yoder KE, Crowell KR, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics*. 2004;114(1):e85-e90. doi:10.1542/peds.114.1.e85.

20. Martinez Gallardo F, López Fiesco A, Zamora G. Symptomatic treatment of common cold in children with a new combination of naproxen sodium plus pseudoephedrine hydrochloride: a comparative trial against pseudoephedrine syrup. *Proc West Pharmacol Soc*. 1994;37:157-158.

21. Sakchainanont B, Ruangkanchanasetr S, Chantarojanasiri T, Tapasart C, Suwanjutha S. Effectiveness of antihistamines in common cold. *J Med Assoc Thai*. 1990;73(2):96-101.

22. Unuvar E, Yildiz I, Kilic A, et al. Is acetaminophen as effective as an antihistamine-decongestant-acetaminophen combination in relieving symptoms of acute nasopharyngitis in children? a randomised, controlled trial. *Int J Pediatr Otorhinolaryngol*. 2007;71(8):1277-1285.

23. Eccles R. The powerful placebo in cough studies? *Pulm Pharmacol Ther*. 2002;15(3):303-308.

24. healthychildren.org. Botulism. http://www.healthychildren.org/English/health-issues/conditions/infections/Pages/Botulism.aspx. Accessed September 9, 2014.

25. Vicks Care Center. VapoRub topical ointment. http://www.vicks.com/products/vapo-family/vaporub-topical-ointment. Accessed September 9, 2014.

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Tunisia Johnson on 06/14/2023

KINDERFARMS Ex. 1043
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

Page 7 of 7