Supplementary Online Content

Nurko S, Saps M, Kossovsky J, et al. Effect of open-label placebo on children and adolescents with functional abdominal pain or irritable bowel syndrome: a randomized clinical trial. *JAMA Pediatr.* Published online January 31, 2022. doi:10.1001/jamapediatrics.2021.5750

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Demographic and Baseline Characteristics of FAP vs IBS Patients
There were significant differences in Bowel movement frequency (p=0.04); % hard stool (p=0.03), prior use of laxatives (p=0.02) and FDI (p=0.04)

	FAP	IBS
Sample size	16 (53.3%)	14 (46.7%)
Age (years)	14.3 ± 0.6	13.8 ± 1.1
Number (%) female	11 (68.8%)	13 (92.9%)
Duration of symptoms (years)	3.4 ± 0.7	3.1 ± 0.9
Pain intensity at baseline (0-100 VAS)	48.7 ± 3.4	42.5 ± 4.6
Bowel movement frequency/week	3.3 ± 0.2	1.5 ± 0.1
% hard stools	8.5 ± 4.3	28.5 ± 9.2
Functional Disability Inventory (FDI)	6.7 ± 1.4	12.7 ± 1.9
Moderate or severe disability on FDI	3 (18.7%)	6 (42.8%)
Anxiety (RCADS)	5 (31.2%)	8 (57.1%)
Pediatric Quality of Life (PedsQL)	59.1 ± 1.8	53.8 ± 2.6
PedsQL Gastrointestinal Symptoms Scale	78.1 ± 2.6	69.1 ± 1.7
Child Depression Inventory (CDI) score	10.0 ± 2.0	12.5 ± 1.6
Prior use of Cognitive Behavioral Therapy	4 (25.0%)	7 (50.0%)
Number of current medications	2.5 ± 0.7	3.2 ± 0.5
Prior use of Neuromodulation	1 (6.25%)	4 (28.5%)
Prior use of Laxatives	0 (0.0%)	9 (64.2%)
Prior use of proton pump inhibitors	3 (18.8%)	5 (35.7%)
Prior use of hyoscyamine	4 (25.0%)	6 (42.8%)

Note. All values are means ± standard deviations (SD) or number (percent) as noted in the table.
VAS = Visual Analog Scale, RCADS = Revised Child Anxiety and Depression Scales.

eTable 2. Number of Hyoscyamine Pills Taken as Rescue Medication During the Control and Placebo Periods

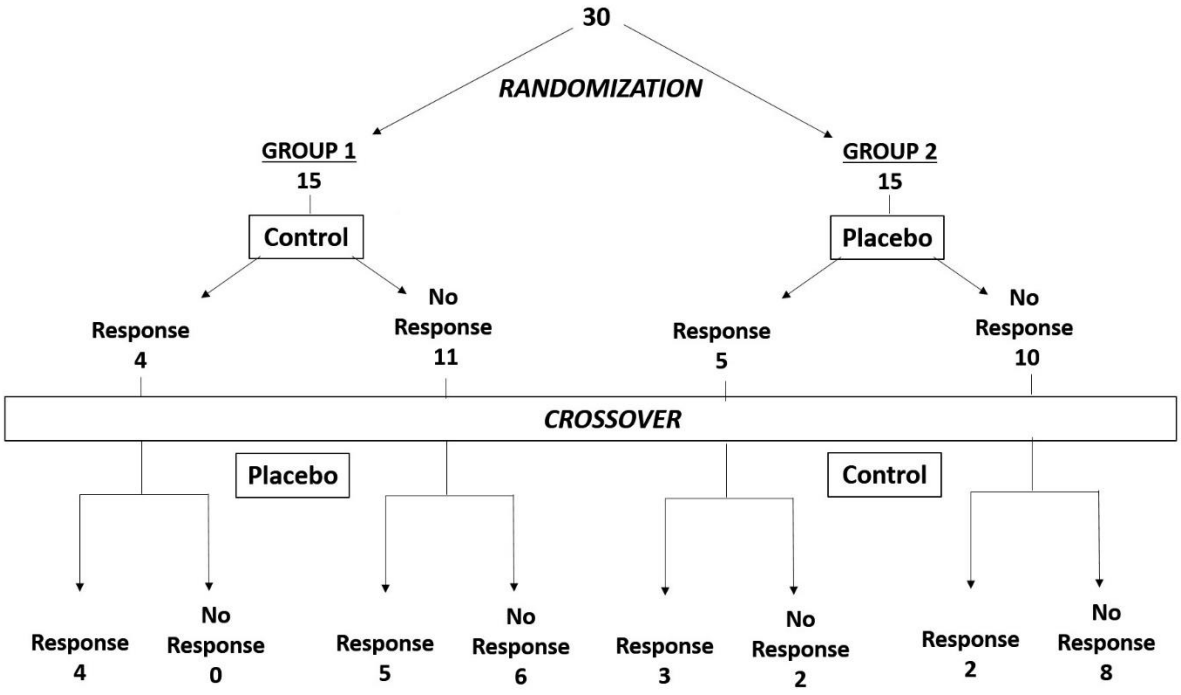
Patient	Control	Placebo	Difference
1	20	3	17
2	13	7	6
3	12	7	5
4	8	3	5
5	5	0	5
6	11	7	4
7	3	0	3
8	2	0	2
9	2	0	2
10	4	3	1
11	3	2	1
12	3	2	1
13	2	1	1
14	2	1	1
15	2	1	1
16	1	0	1
17	12	12	0
18	5	5	0
19	4	4	0
20	0	0	0
21	0	0	0
22	0	0	0
23	0	0	0
24	0	0	0
25	0	0	0
26	0	0	0
27	0	0	0
28	0	0	0
29	0	1	-1
30	0	1	-1

Note. This table shows the number of hyoscyamine pills that each patient took as rescue medication during the no treatment control period and during the open placebo period. The last column shows the difference in the number of pills taken during each time period, with positive numbers indicating that patients took more rescue medications during the control period. The pattern of differences indicates that patients needed more rescue medication during the control period as compared to placebo period. Since the data are skewed, the Wilcoxon signed ranks test (the nonparametric equivalent of a paired samples t-test) was used to analyze the data. The test was statistically significant ($Z=3.34$, $p=.001$).

eTable 3. Global Improvement at the End of the Placebo and Control Periods

Patient	Placebo	Control	Difference
1	3=Better	1=Worse	2
2	3=Better	2=Same	1
3	3=Better	2=Same	1
4	3=Better	2=Same	1
5	3=Better	2=Same	1
6	3=Better	2=Same	1
7	3=Better	2=Same	1
8	2=Same	1=Worse	1
9	3=Better	3=Better	0
10	3=Better	3=Better	0
11	3=Better	3=Better	0
12	3=Better	3=Better	0
13	3=Better	3=Better	0
14	3=Better	3=Better	0
15	3=Better	3=Better	0
16	2=Same	2=Same	0
17	2=Same	2=Same	0
18	2=Same	2=Same	0
19	2=Same	2=Same	0
20	2=Same	2=Same	0
21	2=Same	2=Same	0
22	2=Same	2=Same	0
23	2=Same	2=Same	0
24	2=Same	2=Same	0
25	2=Same	2=Same	0
26	2=Same	3=Better	-1
27	2=Same	3=Better	-1
28	1=Worse	2=Same	-1
29	1=Worse	2=Same	-1
30	1=Worse	2=Same	-1

Note. Global improvement was assessed by a single question that asked whether the patient felt Better, the Same, or Worse at the conclusion of each time period (see the Methods for additional details). These ordinal data were coded 3=Better, 2=Same, and 1=Worse. The last column shows the difference between the placebo and control periods. Positive numbers indicate that the patient reported a higher level of global improvement during the placebo period as compared to control. These ordinal data were analyzed with a Wilcoxon signed ranks test (the nonparametric equivalent of a paired samples t-test). Despite the fact that the table shows a pattern of data that appears to favor placebo over control, the test was not statistically significant (Z=1.00, p=.34).



eFigure. Individual Responses According to the Initial Randomization

Group 1 = Control, then Placebo; Group 2 = Placebo then Control

eAppendix 1. Specifics of Placebo Implemenation and Explanations

A standardized method for explaining the placebo and mind-body connection was used at all sites. The characteristics of the interaction with providers were identical during both periods of the study. The scripts were designed to insure full, ethical disclosure regarding the true nature of the placebo, while also engendering realistic but positive, open-minded attitudes towards the experiment. Equipoise was maintained throughout the study; no one was told that the treatment would "work." To minimize the effects of the patient-physician interaction, the time and interaction style for both groups was similar.

Physician consistency and fidelity

Before the study started, we wrote a detailed script for each visit of each arm. The scripts were discussed and practiced with all team members to ensure they were delivered in the same way to all patients. Given the multicenter nature of the trial, a video was created and distributed to the centers, and one of the investigators from the BCH team (JK) traveled to each center to ensure uniformity in delivery. The interviews were also videotaped to ensure that all providers introduced the placebo period in a similar way. One member of the team (either JK or SN) then witnessed the delivery at all sites to ensure uniformity.

Placebo concepts:

During the enrollment visit we introduced the general concept of a placebo, which was truthfully described as an inert or inactive suspension, like "sugar pills", without any medication in it that in blinded randomized controlled trials (RCTs) often produced benefit.

Script for randomization to placebo:

At the visit in which families were randomized to placebo, the following seven concepts were discussed: a) the placebo effect is powerful in randomized clinical trials; b) although we have much more to learn about how it works, we do know that it takes advantage of the mind-body connection; c) one reason for its effect may be that the body automatically responds to taking the placebo suspension and activates responses that help reduce pain and swelling; d) the placebo jump-starts this beneficial response; e) another good thing about a placebo is that you do not need to believe in it for it to work – a positive attitude helps, but is not necessary; f) however, for the placebo to work, it is important that you to take the suspension on a regular basis, and finally g) the great thing about placebos is that there are no side effects.

Placebo administration

Our placebo mimicked the appearance of many medications used in pediatric care. To avoid the possibility of patients being unable to swallow a pill, we used an inert suspension (HUMCO™ Simple Syrup; Texarkana, TX) containing 85% sucrose, citric acid, purified water, and methyl paraben as a preservative. Patients were instructed to take 1.5 ml, given with a 3 ml plastic syringe. The suspension was prepared by the research pharmacy of each institution. We chose an opaque medication bottle typically used for the routine prescription of liquid medication.

Families were given a typical prescription medicine bottle that contained the placebo suspension with a pharmacy label that had the patient's name and the words "placebo suspension", as well as directions for use: take 1.5 ml twice a day. They were also given individual 3 ml syringes and were shown with extreme care how to measure the placebo dose of 1.5 ml. They were then instructed to take the first dose of placebo in the office. The placebo was prescribed twice daily.

eAppendix 2. Other Outcomes

Bowel movement characteristics

The mean baseline bowel movements per week was 1.6 ± 0.1. There was no significant difference in bowel movement frequency during OLP vs CP (1.9 ± 0.2 vs 1.7 ± 0.1; p=0.3), or when comparing the characteristics of bowel movements between time periods. The baseline Bristol stool score was 3.1 ± 0.8 after baseline week, 2.8 ±1.4 after the CP and 3.1 ± 1.3 after OLP (p=0.3).

Functional Disability

There was a significant improvement in functional disability at the end of the study compared with baseline (75% of subjects having no or minimal disability at week 6 (p=0.04).There was no difference in the response comparing the periods of CP (32%) with OLP (32%), or the randomization order.

Quality of life (QOL)

There was a significant improvement in overall QOL by PedsQL comparing the baseline to the end of the study, according to both the children (56.7 ± 1.6 to 76.3 ± 2.8, p=0.01) and parents (62.9 ± 2.8 to 73.3 ± 2.9, p=0.001), and a significant improvement in the worst pain intensity comparing the baseline to the end of the study, according to both children (73.2 ± 3.4 to 67.4 ± 4.7, p=0.02) and parents (73.9 ± 4.8 to 62.4 ± 5.2, p=0.04). There was no difference on GI specific QOL scores comparing the baseline to the end of the study according to the children (73.9 ± 1.8 vs. 70.8 ± 2.7, p=0.2), but there was a significant difference according to the parents (63.4 ± 2.2 vs. 71.9 ± 2.8, p=0.006).

There was no difference in GI QOL at the end of the study comparing those patients that responded to placebo to those that did not respond to placebo, according both the children (73.3 ± 5.1 vs 79.0 ± 2.8, p=0.3, and 73.8 ± 4.2 vs 68.3 ± 3.4, p=0.3, respectively) and the parents: (74.7 ± 6.0 vs 73.2 ± 4.3, p =0.8 and 75.5 ± 4.9 vs 69.3 ± 3.4, p=0.29, respectively). There was a significant difference in abdominal pain QOL at the end of the study comparing those that responded to placebo to those with no response according to both the children (62.6 ± 8.8 vs 71.8 ± 4.8, p=0.04) and the parents (53.9 ± 7.7 vs 64.6 ± 7.2, p=0.04).

Expectations

Children. There was significantly higher overall expectation that the placebo would have a beneficial effect on pain as compared to the CP (44% vs 12%, p<0.05). However, at the end of the study, there was no significant relationship between the response to the placebo and the initial expectation, as 63% of those that improved with placebo expected it would be beneficial, while 43% of those that did not expect an improvement showed improvement by the end of the trial (p= 0.3). Twelve percent of the patients thought there could be an excellent response, and of those, 30% responded while 54% of those that did not expect an excellent improvement responded (p 0.4).

Parents. Eighty-six percent of the parents had an expectation that the placebo would have an effect. However, there was no relationship between response to the placebo and the initial parental expectation, as 26% of those that thought there would be any improved with placebo had improvement, while 30 % of those that did not expect an

improvement improved (p=0.8). Fifty percent of the parents thought there could be an excellent response, and of those, 36% responded while 18% of those that were not expecting an excellent improvement responded (p=0.3).

Overall, children tended to have less expectations of success as opposed to the parents. There was concordance that the placebo would have any effect in 47% of the pairs, while in 52% of the cases the parents thought it would be effective and the children did not (p=0.3).