

# The Placebo Response in Pediatric Abdominal Pain-Related Functional Gastrointestinal Disorders: A Systematic Review and Meta-Analysis

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**Objective** To investigate the magnitude and determinants of the placebo response in studies with pediatric abdominal pain-related functional gastrointestinal disorders.

**Study design** The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and CINAHL were searched for systematic reviews and randomized placebo-controlled trials concerning children 4-18 years of age with an abdominal pain-related functional gastrointestinal disorder. The primary outcome was the pooled proportion of subjects assigned to placebo with improvement as defined by the authors. The effect of trial characteristics on the magnitude of the placebo response was investigated using univariate meta-regression analysis.

**Results** Twenty-one trials were identified. The pooled proportion of subjects with improvement was 41% (95% CI, 34%-49%; 17 studies) and with no pain was 17% (95% CI, 8%-32%; 7 studies). The pooled standardized mean difference on the Faces Pain Scales compared with baseline was  $-0.73$  (95% CI,  $-1.04$  to  $-0.42$ ; 8 studies). There was significant heterogeneity across studies with respect to both outcomes. Lower dosing frequency ( $P = .04$ ), positive study ( $P = .03$ ), longer duration of treatment ( $P < .001$ ), and higher placebo dropout ( $P < .001$ ) were associated with higher report of no pain. Response on Faces Pain Scales was greater in studies conducted in the Middle East ( $P = .002$ ), in studies that did not report the randomization schedule ( $P = .02$ ), and in studies with a higher percentage of females ( $P = .04$ ).

**Conclusions** Approximately 41% of children with abdominal pain-related functional gastrointestinal disorders improve on placebo. Several trial characteristics are correlated significantly with the proportion of patients with no pain on placebo and with the magnitude of the placebo response on Faces Pain Scales. These data could be valuable for the design of future studies. (*J Pediatr* 2017;■■■:■■■-■■■).

Chronic abdominal pain is one of the most common complaints in childhood, accounting for 2%-4% of pediatric office visits.<sup>1</sup> In most cases, no evidence of an organic cause can be found. These children are usually diagnosed with one of the abdominal pain-related functional gastrointestinal disorders (AP-FGIDs), which affect approximately 13.5% of all children.<sup>2,3</sup> The most common AP-FGIDs are irritable bowel syndrome (IBS), functional dyspepsia, and functional abdominal pain, with a respective prevalence of 8.8%, 4.5%, and 3.5%.<sup>3</sup>

Several systematic reviews evaluated the response of children and adults with AP-FGIDs on pharmacologic treatment and demonstrated benefit of some pharmaceutical agents, including peppermint oil, antidepressants, 5-HT<sub>3</sub> receptor antagonists, 5-HT<sub>4</sub> receptor agonists, cyproheptadine, and famotidine.<sup>4-7</sup> However, these reviews demonstrated a lack of evidence to support the routine use of any of these pharmacologic treatments. Of remarkable notice is the large proportion of children and adults with AP-FGIDs who respond to placebo in clinical trials.<sup>8</sup> A placebo response is defined as the outcome caused by a placebo manipulation. It includes the "true placebo effect" and other factors, such as natural course of the disease, spontaneous symptoms fluctuations, and regression to the mean.<sup>9,10</sup> Meta-analyses of randomized controlled trials (RCTs) in adult patients with IBS revealed an average placebo response rate of 36.0%-42.6%.<sup>11-14</sup> This high placebo response rate has important implications for both researchers and clinicians. First, a high placebo response results in reduced assay sensitivity (ie, the ability of a trial to detect true differences between active treatment and placebo) and may thus lead to inefficient trials. In clinical practice, in contrast, the placebo response can be considered a valuable and powerful clinical tool.<sup>15</sup>

Indeed, it could be argued that clinicians should aim to maximize the placebo response to enhance patient benefit from any treatment strategy, because maximal efficacy is desirable irrespective of whether improvements are based on specific

AP-FGID	Abdominal pain-related functional gastrointestinal disorder
CENTRAL	Cochrane Central Register of Controlled Trials
FPS	Faces Pain Scales
IBS	Irritable bowel syndrome
RCT	Randomized controlled trial

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treatment effects, placebo mechanisms, or a combination.<sup>16</sup> Thus, the identification of determinants of the placebo response is important for both clinical trial design and clinical practice.

Meta-analyses of studies in adults with AP-FGIDs have identified several variables affecting the placebo response in clinical trials, including entry criteria,<sup>13</sup> number of office visits,<sup>13</sup> body mass index,<sup>17</sup> a consistent symptom pattern,<sup>17</sup> duration of therapy,<sup>12</sup> country of trial origin,<sup>12</sup> and outcome assessor.<sup>12</sup> Data on the magnitude and determinants of the placebo response in pediatric patients with AP-FGIDs are lacking. Therefore, we aimed to investigate the magnitude and determinants of the placebo response in trials on pediatric patients with AP-FGIDs.

## Methods

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and CINAHL databases were systematically searched for studies on AP-FGIDs from inception up to April 2016. The full search strategy is provided in the [Appendix](#) (available at [www.jpeds.com](http://www.jpeds.com)).

Criteria for the inclusion of studies were: (1) study was an RCT comparing the effect of placebo with any pharmacologic or nonpharmacologic treatment, (2) study population consisted of children within the age range of 4-18 years, with (3) a diagnosis of chronic or recurrent abdominal pain, IBS, functional dyspepsia, functional abdominal pain, functional abdominal pain syndrome, or abdominal migraine as defined by the authors. Exclusion criteria were: (1) language other than English, Dutch, German, French, Danish, or Spanish, (2) studies including patients with an organic cause for abdominal complaints (including but not limited to inflammatory bowel disease, peptic ulcer), and (3) studies including patients with acute abdominal pain.

First, the eligibility of studies was determined independently by 2 reviewers based on the titles and abstracts. Any disagreement between the reviewers was resolved by consensus. Afterward, full-text evaluation was performed of all studies that were identified as potentially eligible to assess if they fulfilled the inclusion criteria.

### Data Extraction and Validity Assessment

As outcome measures, the proportion of patients with improvement as defined by the authors, the proportion of patients with no pain, and baseline and end-of-treatment symptom severity as determined using Faces Pain Scales (FPS)<sup>18</sup> were extracted independently by 2 reviewers from each study. Furthermore, the following study characteristics were extracted using structured forms: year of publication, geographical location, trial setting (ie, monocenter or multicenter), criteria used to define AP-FGIDs, mean or median age of participants at inclusion, dosing schedule of the placebo, timing of outcome assessment, assessor of primary outcome (ie, patient, parent, or physician reported), generation of randomization schedule, concealment of allocation and the study design, mode

of administration of the placebo, positive study (ie, a statistically significant effect of the active agent compared with the placebo based on the primary outcome), percentage of females in the placebo group, and dropout rate in the placebo group. Dichotomous outcome measures were categorized as either improvement or no pain. The overall quality of the studies was assessed using the Jadad scale.<sup>19</sup> Data were extracted from the intention-to-treat population of each included study. If outcomes were reported on multiple time points, end-of-treatment data were analyzed.

### Data Analyses

Meta-analysis was conducted using Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, New Jersey). Data were pooled using a random effects model. Heterogeneity was assessed with the Cochran Q statistic, the  $\tau^2$  statistic and the  $I^2$  statistic. The  $\tau^2$  statistic represents the between-study variance and a value of  $>1$  suggests the presence of substantial heterogeneity among studies. The  $I^2$  statistic describes the percentage of the total variation across studies. An  $I^2$  value of  $>50\%$  and a  $P$  value of  $<0.05$  indicated significant heterogeneity.<sup>20,21</sup> The primary outcome was the pooled proportion of patients assigned to placebo with improvement as defined by the authors, with a 95% CI. Secondary outcome measures were the pooled proportion with no pain and the pooled standardized mean difference on the FPS compared with baseline in patients receiving placebo. To assess the correlation between study characteristics and the placebo response, univariate meta-regression was conducted for each of the study characteristics discussed. Multivariate meta-regression analysis was not performed owing to the limited number of included studies.

## Results

The search yielded 1669 potentially relevant articles and abstracts. Another 2 articles and abstracts were identified by hand search. A total of 599 records were duplicates ([Figure 1](#); available at [www.jpeds.com](http://www.jpeds.com)). Of the remaining 1072 records, 1026 were excluded based on the screening of titles and abstracts. A total of 46 records were reviewed in full text, which led to the exclusion of another 25 records there were no relevant outcome measures ( $n = 8$ ),<sup>23-30</sup> it was a conference abstract of a study that has been published in full text ( $n = 4$ ),<sup>31-34</sup> it was a conference abstract that has been published twice repeatedly ( $n = 2$ ),<sup>35,36</sup> it used an adult study population ( $n = 3$ ),<sup>37-39</sup> there were multiple manuscripts concerning the same placebo group (in a multidrug multi-arm study;  $n = 2$ ),<sup>40-42</sup> there was no therapeutic RCT ( $n = 2$ ),<sup>43,44</sup> no AP-FGID were included ( $n = 1$ ),<sup>45</sup> the placebo was given in combination with other drug ( $n = 1$ ),<sup>46</sup> the exact numbers for outcome measures not provided ( $n = 1$ ),<sup>47</sup> or it was a conference abstract with insufficient data to include in the analysis ( $n = 1$ ).<sup>48</sup> Two conference abstracts were included after additional information was provided from the authors (personal communication).<sup>49,50</sup> In total, 21 records were included in the qualitative synthesis.<sup>42,49-68</sup>

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