Double-blind Placebo-Controlled Trial of Amitriptyline for the Treatment of Irritable Bowel Syndrome in Adolescents

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Objectives To determine the efficacy of amitriptyline (AMI) in treating irritable bowel syndrome (IBS) in adolescents.

Study design Adolescents 12 to 18 years with newly diagnosed IBS were surveyed with a symptom checklist, pain rating scale, visual analog scale, and IBS quality of life (QOL) questionnaire. Subjects were randomized in a double-blinded fashion to receive AMI or placebo, and again completed surveys at 2, 6, 10, and 13 weeks.

Results Thirty-three patients (24 female) were enrolled. Patients receiving AMI were more likely to experience improvement from baseline in overall QOL at 6, 10, and 13 weeks (P = .019, .004, and .013). Patients receiving AMI were also more likely to experience a reduction in IBS-associated diarrhea at 6 and 10 weeks (P = .029 for both), a reduction in periumbilical pain at 10 weeks (P = .018), and a reduction in right lower quadrant pain at 6, 10, and 13 weeks (P = .014, .039, and .004).

Conclusion AMI significantly improves overall QOL in adolescents with IBS and should be a therapeutic option for adolescents with this disorder. *(J Pediatr 2008;152:685-9)*

Chronic abdominal pain commonly occurs in adolescents, affects up to 13% of middle school and 17% of high school students, and is severe enough to interfere with activities of daily living in approximately 21% of students overall. In addition, 6% of middle school and 14% of high school students fulfill the criteria for irritable bowel syndrome (IBS).[1] IBS, defined between 1999 and 2006 by the Rome II Criteria, is a type of functional gastrointestinal disorder (FGID) of childhood characterized by at least 3 months in the preceding 12 months of abdominal discomfort or pain described by 2 of 3 features: relieved with defecation, onset associated with a change in frequency of stool, and onset associated with a change in the form (appearance) of stool. In addition, there cannot be structural or metabolic abnormalities to explain the symptoms.[2,3]

In the pediatric age group, only peppermint oil has been evaluated in a placebo-controlled fashion for its effect in children with IBS. Enteric-coated, pH-dependent peppermint oil capsules were shown to reduce the severity of pain in 75% of these children, significantly more than those who received placebo.[4]

Amitriptyline (AMI), a tricyclic antidepressant (TCA), has been shown in adults with IBS to be significantly more effective than placebo in producing global improvement, increasing feelings of well-being, reducing abdominal pain, and increasing satisfaction with bowel movements.[5] The effect of AMI on pediatric patients with IBS has yet to be reported. The aim of this study, therefore, was to prospectively establish the utility of AMI for the treatment of adolescents with IBS, with overall quality of life (QOL) used as a primary outcome measure.

METHODS

During the years 2002-2005, adolescents between the ages of 12 and 18 years, with newly diagnosed IBS based on Rome II criteria were eligible for participation in this double-blind, placebo-controlled study. Patients were excluded from participation if they were receiving any concurrent pharmacotherapy for depression, anxiety, or chronic pain syndromes. All participants were recruited from a suburban, outpatient, private-practice pediatric gastroenterology clinic in Encino, California. The study protocol was preapproved by the Institutional Review Board/Human Subjects Protection Committee at the University of California–Los Angeles. After review of the study protocol, informed consent was obtained by both the subject and a parent or legal guardian.

The 13-week study period involved 3 phases: 2 weeks of enrollment and symptom scoring, 8 weeks of therapy with AMI or placebo, and 3 weeks of "washout" and symptom scoring. On entrance into the study, subjects underwent a clinical evaluation and elec-

AMI	Amitriptyline	QOL	Quality of life
FGID	Functional gastrointestinal disorder	SSRI	Selective serotonin reuptake inhibitors
IBS	Irritable bowel syndrome	TCA	Tricyclic antidepressant
PRS	Pain-rating scale		

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trocardiography to screen for idiopathic long QT syndrome. Although this study used doses of AMI far lower than those in which serious toxic cardiac effects have been reported in patients with underlying idiopathic long QT syndrome,[6] electrocardiograms were obtained as a precautionary measure. Patients were also weighed at weeks 2 and 10.

At weeks 0 and 2, patients were asked to complete data collection packets. All of these packets were self-administered to avoid interview bias. Each data collection packet contained the following: (A) An IBS-QOL Questionnaire. This 34-question form, validated in adults, was used for psychometric analysis of 7 subscales, including dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, relationships, and overall score in patients with IBS. Two questions regarding the subscale of sexual activity were omitted.[7] Improvement in overall QOL score was the primary outcome variable[8]; (B) A symptoms checklist. This checklist was used to assess 13 IBS-associated symptoms. Patients were asked to place a checkmark next to each symptom that applied to them[9]; (C) A pain-rating scale/Likert-Like Scale (PRS). This scale was used to assess the extent to which the subject's pain interfered with specific activities of daily living (eg, school work, socializing with friends, sports). Scores ranged from 0 (never) to 6 (always)[10]; and (D) A visual analog scale. This scale was used to assess the subject's pain intensity and frequency on a scale of 0 to 10. For intensity, 0 signified no pain, and 10 signified the worst pain possible. For frequency, 0 signified never and 10 signified constant. These notations were measured in mm from point 0.[11]

From weeks 3 through 10, subjects were randomized in a double-blinded, placebo-controlled fashion to receive AMI or placebo and were again asked to complete data collection packets at weeks 6 and 10. Those patients undergoing AMI therapy received the following doses on the basis of their body mass: (A) 30 to 50 kg—one 10-mg capsule by mouth at bedtime; (B) 50 to 80 kg—two 10-mg capsules by mouth at bedtime; and (C) 80 kg—three 10-mg capsules by mouth at bedtime.[12]

From weeks 11 through 13, patients did not receive AMI or placebo. They were again asked to complete a data collection packet at week 13. The study period ended with the completion of the final data collection packet.

Statistical Methods

Repeated measure analysis of variance was used to obtain parametric *P* values. The Wilcoxon signed rank test and χ^2 test were used to obtain the nonparametric *P* values.

RESULTS

Thirty-three adolescents (24 female) with a new diagnosis of IBS on the basis of Rome II criteria completed the trial. Seventeen patients received placebo, and 16 patients received AMI. The mean ages of the placebo and AMI groups were 14.2 years and 15.3 years, respectively ($P = .08$). The mean intensity of pain at baseline in the placebo and AMI groups was 64.6% and 65.9%, respectively ($P = .9$), and the mean overall QOL scores at baseline were 127.5 and 109.4, respectively ($P = .05$).

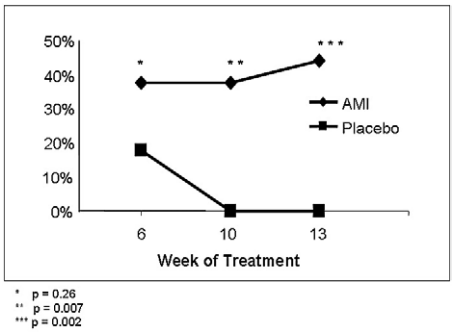

Figure 1. Percent of IBS patients in AMI and Placebo groups with at least 15% improvement from baseline in overall QOL score.

An additional 2 patients who fulfilled inclusion criteria and agreed to participate in the trial dropped out before week 3 to receive AMI in an open fashion outside of the study. No patients were excluded because of QT interval abnormalities on the electrocardiogram, and no patients dropped out after starting treatment.

Mean overall QOL scores in the AMI group at weeks 6, 10, and 13 were 127.6, 128.0, and 126.2, respectively, and in the placebo group were 132, 129.4, and 129.8, respectively. When compared with time 0, subjects receiving AMI were significantly more likely than those receiving placebo to experience at least a 15% improvement in overall QOL score at 10 and 13 weeks ($P = .007$ and $P = .002$, respectively [Figure 1]), and to experience an improvement in overall QOL score at 6, 10, and 13 weeks ($P = .019$, .004, and .013, respectively [Figure 2]). Subjects receiving AMI were also significantly more likely to experience an improvement in dysphoria at 10 and 13 weeks ($P = .003$ and .014, respectively), interference with activities at 6 and 10 weeks ($P = .03$ and .003, respectively), health worry at 10 and 13 weeks ($P = .024$ and .0002, respectively), and food avoidance at 6 and 10 weeks ($P = .008$ and .007, respectively [Table I]). No significant improvement was noted for these specific subscales or overall score after time 0 when compared with any other recorded time ($P > .05$).

When compared with time 0, subjects receiving AMI were not significantly more likely than those receiving placebo to experience an improvement at any recorded time in body image, social reaction, and relationships ($P > .05$). When compared with time 0, subjects receiving AMI were significantly more likely than those receiving placebo to experience a reduction in IBS-associated diarrhea at 6 and 10 weeks ($P = .029$ at both intervals). Subjects receiving AMI were also significantly more likely to experience a reduction in periumbilical abdominal pain at 10 weeks ($P = .018$), and in right lower quadrant abdominal pain at 6, 10, and 13 weeks ($P = .014$, .039, and .004, respectively [Table II]).

When compared with time 0, no significant reduction was found between the AMI and placebo groups at any recorded time for the following FGID-associated symptoms: headache,

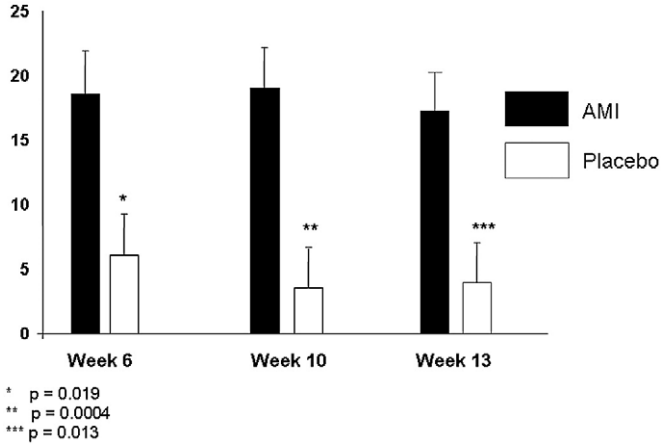

Figure 2. Change in overall QOL scores from week 0 in AMI vs. Placebo treated IBS Patients (mean ± SEM).

Table I. Change in QOL subscale scores from week 0 in patients with IBS treated with AMI versus placebo

	Dysphoria	Interference with activity	Health worry	Food avoidance
Week 6				
AMI	6.1 ± 5.7	4.8 ± 3.9	1.2 ± 1.8	1.6 ± 2.1
Placebo	2.7 ± 4.6	1.5 ± 4	0.2 ± 1.5	−0.5 ± 2.1
P value	.07	.031	.088	.008
Week 10				
AMI	6.7 ± 5.4	5.1 ± 4.7	1.6 ± 1.8	1.9 ± 0.5
Placebo	1.1 ± 5.1	0.7 ± 4.7	0.3 ± 1.3	−0.2 ± 2.2
P value	.003	.003	.024	.007
Week 13				
AMI	5.7 ± 7.7	4 ± 5.2	2 ± 2.2	1 ± 0.7
Placebo	1.1 ± 5.4	1.2 ± 3.7	−0.1 ± 1.1	−0.1 ± 2.3
P value	.014	.063	.0002	.14

When compared with time 0, there were no differences between the 2 groups in body image, social reactions, and relationships.

backache, nausea, dizziness, weakness, constipation, presence of mucous in the stool, tenesmus, pain relief after defecation, pain exacerbation with defecation, abdominal distension, diffuse abdominal pain, midepigastric pain, lower abdominal pain, left lower quadrant pain, right upper abdominal pain, and left upper abdominal pain. In addition, no significant differences were found in the intensity or frequency of abdominal pain or in interference with schoolwork, sports, or friends ($P > .05$). No subanalyses of responses to treatment between sex and age groups were performed because the sample size was too small.

Mean weight gain between weeks 2 and 10 was 1.4 kg in the AMI group and 1.6 kg in the placebo group ($P > .05$). Although symptom scoring did not specifically address worsening fatigue during the trial, subjects did not complain of an exacerbation of this symptom at the doses used in the study. No other side effects were reported.

Table II. Percent change in symptoms from week 0 in patienets with IBS treated with AMI versus placebo

	IBS-associated diarrhea	Periumbilical pain	RLQ pain
Week 6			
AMI	−50 ± 12.9	−18.8 ± 10.1	−25 ± 14.4
Placebo	−11.8 ± 11.8	5.9 ± 10.4	17.6 ± 9.5
P value	.029	.089	.014
Week 10			
AMI	−50 ± 12.9	−12.5 ± 8.5	−12.5 ± 8.5
Placebo	−11.8 ± 11.8	17.6 ± 9.5	11.8 ± 8.1
P value	.029	.018	.039
Week 13			
AMI	−37.5 ± 12.5	−12.5 ± 12.5	−25 ± 11.2
Placebo	−11.8 ± 11.8	17.6 ± 9.5	17.6 ± 9.5
P value	.134	.055	.004

DISCUSSION

We conducted a prospective, double-blind, placebo-controlled evaluation of AMI for its effect on IBS in a pediatric age group. The primary limitation of the study was the number of participants. We did find a significant improvement in overall QOL in the patients who received AMI. However, when trying to identify improvement in specific IBS-associated symptoms, we only found significant differences in periumbilical pain, right lower quadrant pain and IBS-associated diarrhea. We hypothesize that the improvement in diarrhea may have been due to the anticholinergic effect of AMI, but are unsure why we found improvement in periumbilical and right lower quadrant pain specifically and not pain in other locations. It also remains unclear why differences were found between some treatment weeks but not others. With a larger cohort of patients, we anticipate that additional significant differences in FGID-associated symptoms and in QOL measurements between populations, as well as differences at additional time periods, may be determined. In addition, we might have been able to ascertain differences in response to therapy between sex and age groups.

Interestingly, more than half of the eligible adolescents or their guardians refused to participate in the study. Their primary reason for this decision was not because of the possibility of receiving placebo instead of AMI, nor was it because of the duration of the study and its associated pretreatment period in the face of a strong desire for immediate symptom relief. Instead, parents most often felt uncomfortable with the potential use of an antidepressant medication of any kind for their child, citing negative reports in the lay press[13,14] as the determining factor in their decision-making process. This effect was amplified in 2004 after the United States Food and Drug Administration issued formal "black box" warnings regarding the increased potential for "suicidality" in children consuming antidepressant medications, including AMI,[15] and resulted in antidepressant use in children dropping 20% between 2004 and 2006.[16,17]

The doses of AMI (and other TCAs) used in this and other adult IBS and pain syndrome studies were typically far less than those used to treat depression.[5,18-21] When administered at this level, AMI is believed to work primarily by inducing pain tolerance through peripheral or central antinociceptive properties as well through its anticholinergic effects,[5] and secondarily through its anxiolytic effects. Given these observations, when used at lower doses, perhaps AMI should no longer be termed an "antidepressant" or "psychotropic" medication, but rather one to treat neuropathic pain associated with chronic pain syndromes.

Another limitation of the study was its length. The decision to treat patients for only 8 weeks was based on information from previous adult studies. The data suggested that this length would be adequate to determine a sustained response, and, at the same time, short enough to minimize patient dropout.[5,22,23] Of the 16 patients who received AMI, 14 elected to continue the medication, and all of those who received placebo elected to start therapy with AMI.

In 2006 the Rome III Criteria for Child/Adolescent IBS were established. The most significant change from Rome II Criteria was the reduction in the necessary duration of symptoms from 3 months to 2. This modification was made to better reflect clinical experience in the pediatric age group, to allow primary care physicians to make the diagnosis, and to facilitate clinical research of FGIDs in children.[24] With this change, the prevalence of IBS is likely to increase, and recruitment for future studies, even in the era of black box warnings for antidepressants, should improve.

In addition to TCAs, selective serotonin reuptake inhibitors (SSRIs) represent a promising class of medication that may be used for the treatment of FGIDs in children. SSRIs block the serotonin transporter protein at the level of the presynaptic nerve ending, thereby increasing the synaptic exposure to a higher concentration of hyperalgesia-mediating serotonin.[25,26] Although in animal models SSRIs display weaker effects on nociception than do TCAs, they have fewer anticholinergic side effects, which have made them an attractive alternative to TCAs at higher doses.[25,27]

In conjunction with management of IBS with chronic pain medications, biologic, psychological, and social factors affecting patients with this disorder should be addressed. Collectively-termed the "biopsychosocial" approach, this model suggests that both aberrant gut motility and altered sensation are influenced by genetics, personal experience, and cultural environment, and recommends specifically-targeted cognitive-behavioral therapy.[3,28]

With the new Rome III criteria, the prevalence of IBS is likely to increase. Given the findings of our study, future investigations should appropriately focus on the judicious use of AMI and other chronic pain medications in children with FGIDs to complement biopsychosocial and antibiotic therapy in these patients.[28-30] Large-scale, double-blind, placebo-controlled, multiarmed, dose-stratified trials comparing the effect of placebo with TCAs and SSRIs in this population would be most useful in elucidating optimal dosing and duration of treatment of these drugs, with special consideration given to suicidality and sex.

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50 Years Ago in *The Journal of Pediatrics*

The prevention of bilirubin encephalopathy

Waters WJ. J Pediatr 1958;52:559-65

William J. Waters, MD, a pioneering hematologist-oncologist at Upstate Medical Center in Syracuse, New York, had an intense interest in the pathogenesis and prevention of *bilirubin encephalopathy*, a term he coined in 1953, convinced that bilirubin itself was toxic to the brain.[1] His conclusion derived from suggestions that the yellow central nervous system (CNS) pigment in kernicterus was causally linked to brain damage and the demonstration by Dereymaeker that the physical and chemical character of the pigment were consistent with bilirubin,[2] a finding subsequently independently confirmed by Waters et al[1,3] and Claireaux et al.[4] The report by Waters, published 50 years ago in *The Journal*,[5] built on the understanding of bilirubin as a neurotoxin and focused on treatment considerations that in 1958 remained limited to exchange transfusion; phototherapy would not become a mainstay of hyperbilirubinemia management for more than another decade.

It is of interest that several prominent themes in Waters' 1958 article still resonate with recent discussions on neonatal hyperbilirubinemia; including: (1) the debate regarding the criteria for exchange transfusion; (2) the question of whether total serum bilirubin best predicts the potential for brain injury; and (3) the recognition that hepatic bilirubin clearance capacity contributes significantly to the risk of neonatal hyperbilirubinemia. More specifically, Waters noted that "considerable latitude exists" regarding criteria for exchange transfusion in neonates born to Rh-isoimmunized mothers. He himself adopted an approach predicated on the serum bilirubin level, coupled with an assessment of the neonate's clinical condition and postnatal bilirubinemia trajectory, presaging current newborn exchange transfusion guidelines.[6] The advent of Rh prophylaxis, fetal treatment in isoimmunized pregnancies, the introduction of and improvements in phototherapy, and the postnatal use of intravenous immune globulin to attenuate immune-mediated hemolysis have markedly reduced the current need for exchange transfusion. Presciently, although Waters believed that the "serum bilirubin level reflects best the potentiality of any given infant for brain damage," he pleaded for better predictive measurements. Whether the total serum bilirubin, unbound bilirubin, bilirubin:albumin ratio, or some other measure best indexes the risk of bilirubin-induced neurologic dysfunction remains an area of clinical study and ongoing debate.[7,8] Finally, it is noteworthy that Waters highlighted hepatic bilirubin clearance as an important factor in determining a neonate's risk for marked hyperbilirubinemia, an observation borne out in subsequent clinical study and our growing understanding of the role that hepatic gene polymorphisms play in the genesis of neonatal jaundice.[9-11]

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