Invited Review

Coping with Ignorance: Exploring Pharmacologic Management for Pediatric Functional Abdominal Pain

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INTRODUCTION

Chronic abdominal pain is a common pediatric problem, affecting 7 to 25% of youth (1-3) and accounting for 2 to 4% of pediatric office visits (4). The overwhelming majority of affected children suffer from a functional gastrointestinal disorder (FGID) in that explanatory physical disease in the form of demonstrable structural or biochemical abnormalities is absent (5). Symptom based diagnostic criteria for pediatric FGID are currently applied based on the perceived location of the discomfort and any associated changes in bowel patterns, with the best known FGID associated with pain being irritable bowel syndrome (i.e., functional abdominal pain with at least two of the following characteristics: relief with defecation; change in bowel frequency; change in bowel character) (6). Unfortunately, current nosology is incomplete at best, with less than half of youth with suspected chronic functional abdominal pain meeting formal criteria for irritable bowel syndrome and approximately 25% not meeting criteria for any specific FGID diagnosis (7). Consequently this practical review of pharmacologic interventions will focus on functional abdominal pain (FAP) broadly defined to mean a functional gastrointestinal disorder where abdominal pain or discomfort is the predominant symptom. Few randomized controlled trials have been conducted for pediatric FAP and conclusive evidence for the efficacy of any specific treatment is lacking (2,8,9). Nevertheless, the thoughtful practitioner should have an appreciation of the current state of knowledge in order to better guide patients and families and better inform day to day treatment decisions.

RELEVANCE

Pediatric health care providers know FAP is a vexing problem (10) associated with an excess of functional impairment and perceived health limitations, an overuse of ambulatory health services, and a risk of potentially dangerous and unnecessary investigations and procedures (11-13). It is also clear that the disorder or disorders subsumed under the rubric of FAP are not limited to gastrointestinal pain and distress but that there is a consistent association with other somatic symptoms such as headache (including migraine), physical aches and pains, dizziness, and fatigue. FAP has been consistently associated with high rates of anxiety and/or depressive symptoms and disorders. Approximately 75% of youth presenting with FAP in both primary and specialty care settings have an anxiety disorder. Approximately 40% have depression (14-17,13). Early-onset anxiety and depressive disorders are chronic, recurrent, and disabling in their own right, and confer during life an increased risk of substance abuse, poor work history, school failure, and attempted or achieved suicide (18,19), but are seldom recognized in youth with FAP (10).

RATIONALE FOR PHARMACOLOGIC TREATMENT

The decision to medicate a child with FAP must be considered in the context of our limited knowledge base and must balance the potential risks and benefits of the intervention, including the potential for as yet undetermined long term adverse effects. Although psychotherapeutic interventions have been inadequately studied, it is important to realize that empirical support for the use of psychotherapeutic interventions is equal or even superior to that for any of the commonly used medications. Two small randomized controlled trials of multimodal cognitive behavioral intervention by the same group of investigators found that treated groups improved more quickly, did better functionally, and were more likely to be pain free at 3-month follow up than wait-list controls (20) or those receiving usual care (21). A nonrandomized

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trial of CST also reduced pain, school absence, and health service use in treated children (22). Case reports suggest that operant behavioral interventions (23,24), guided imagery (25), and self-hypnosis (26) may be beneficial. It is nonetheless true that formal psychotherapeutic interventions are not routinely used in the typical pediatric office practice, and primary care clinicians are unlikely to refer children with FAP to mental health professionals or for psychotherapeutic treatment (10). This may reflect sensitivity to stigma, lack of on-site mental health services, lack of faith in mental health professionals, and/or concerns about costs and patient preferences. Children with functional abdominal pain and their families may also be reluctant to agree to psychotherapy due to its perceived inconvenience, cost, or its implication that pain is a mental problem.

Pharmacological management offers the advantages of relative simplicity, economy, and acceptability in the medical setting, and many families prefer such an approach regardless of whether the child is suffering from comorbid anxiety or depression. Pharmacotherapy is more in keeping with and less disruptive to traditional office practice, and offers practical advantages over psychotherapy, which generally requires access to specialized personnel in the practice setting or outside referral.

PHARMACOLOGIC TREATMENT TRIALS

The few randomized controlled medication trials conducted in youth with FAP are summarized below. Conclusive evidence for the efficacy of any single treatment is lacking (2,7,8). Most studies have methodologic limitations and do not address the high rates of other somatic complaints, comorbid anxiety and depressive disorders in these youth. Efficacious and safe medication treatment for FAP would be a significant advance over present practice in which a variety of medications (e.g., tricyclic antidepressants) are being prescribed despite the absence of scientific evidence (27).

Dietary Interventions

Despite suspicions that FAP may be caused by food allergies, low fiber diet or lactose malabsorption, results of dietary interventions (28) and fiber supplementation (29–31) have been disappointing or inconclusive at best (8). Evidence for the effectiveness of dietary fiber or bulking agents is lacking, with an average of 49% of fiber treated subjects improving compared to 40% of those receiving placebo (8). The efficacy of fiber and bulking agents in adults has also not been established despite several trials of variable quality (32).

Antispasmodics

Peppermint oil is thought to cause smooth muscle relaxation via calcium channel blockade. A single twoweek randomized double blind placebo controlled trial of enteric coated peppermint oil capsules in 42 children with pediatric Irritable bowel syndrome reported that 71% of treated patients experienced a reduction in abdominal pain severity compared to 43% of controls (33). Though the study did show improvement in abdominal pain in drug treated subjects, safety and tolerability were not reported and other physical symptoms did not improve with treatment.

H2 Blockers

One double-blind placebo controlled study of the H2– receptor blocker famotidine in 25 children with FAP reported some benefits in a subset of children with dyspeptic (upper tract) symptoms (34). The study reportedly excluded youth with anxiety or depressive disorders, likely limiting its generalizability.

Serotonergic Agents

Medications such as alosetron and tegaserod that interrupt serotonergic neurotransmission in the gut have been shown to be efficacious in adults with irritable bowel syndrome. While a few studies have included adolescents, the drugs have not been studied in children.

A single controlled trial from Europe reported on the use of pizotifen, a serotonin antagonist used for migraine prophylaxis, in children with "abdominal migraine" (essentially functional abdominal pain associated with facial pallor and a family history of migraine) (35). Sixteen children aged 5 to 13 years from a hospital-based clinic were randomly assigned to pizotifen or placebo in a double blind crossover trial. Fourteen subjects completed the trial, with pizotifen treated subjects reporting significantly fewer days of pain, less severe pain, and less overall "misery". Pizotifen was reported to be well tolerated aside from some complaints of drowsiness, lightheadedness, and increased appetite. The drug is not available in the United States. An uncontrolled retrospective chart review suggests that cyproheptadine and propranolol may be promising prophylactic treatments for abdominal migraine and worthy of additional study (36).

Antidepressants and Anxiolytics

Published double blind placebo controlled trials of antidepressant medications for youth with FAP are currently lacking. We first became interested in the selective serotonin reuptake inhibitor (SSRI) citalopram as a treatment for FAP based on anecdotal clinical experience, the high rate of comorbid anxiety and depressive disorders in FAP and an appreciation of the potential role of serotonin in the gut (37). A randomized double blind placebocontrolled trial of the SSRI paroxetine for irritable bowel syndrome in adults unresponsive to high fiber diet also suggested drug efficacy (38). A recent open trial of citalopram found that 21 of 25 (84%) children and adolescents with functional abdominal pain responded to medication based on clinician reports of being "much" or "very much" improved. Additionally, child and parent ratings of abdominal pain, anxiety, depression, other somatic symptoms, and functional impairment all improved significantly over the course of the study compared to baseline (39). Citalopram is a lipophilic tertiary amine exhibiting high specificity and selectivity for serotonin reuptake inhibition. It is characterized by a relatively low likelihood of drug interactions and significant P450 enzyme inhibition (40,41). It can be administered once daily with little need for dose titration or laboratory testing for drug toxicity (42). Citalopram was generally well tolerated, and suicidal thoughts present at study baseline diminished progressively during the study, with no subject reporting suicidal thinking at study endpoint. We are currently conducting a double blind randomized clinical trial comparing citalopram to placebo. While the evidence base for the use of SSRIs for FAP is small, there is a growing body of evidence for their efficacy in the treatment of pediatric anxiety (43,44) and depressive disorders (45,46). Recent warnings of an increased risk of suicidal thinking or behavior in SSRI treated youth indicate that careful clinical monitoring is warranted and additional research is needed.

The recommendation for use of TCAs to treat pediatric FAP has been based primarily on anecdotal experience (27) and positive reports of efficacy in adults with irritable bowel syndrome. The methodologic quality of many studies is poor (32,47). One well done double blind placebo controlled study of desipramine for adults with irritable bowel syndrome did not show a statistically significant difference on intent to treat analysis, but did demonstrate the superiority of desipramine on the primary outcome measure by post hoc completer analysis and analysis taking into account medication compliance (48). Legitimate concerns on the use of TCAs in children and adolescents include potential side effects, a low therapeutic index, an associated risk of sudden death in children, and a lack of efficacy in comorbid pediatric depression (49).

There have been no reports on the use of selective serotonin norepinephrine reuptake inhibitors such as venlafaxine, benzodiazepines, or other anxiolytics such as busiprone for the treatment of pediatric FAP.

VISCERAL HYPERSENSITIVITY AS A POTENTIAL TARGET OF INTERVENTION

A few small studies suggest that youth with FAP or specific FGIDs such as irritable bowel syndrome may be especially sensitive to visceral sensations or discomfort (50,51), and to peripheral physical sensations such as deep muscle pressure as well (52,53). Such "visceral hypersensitivity" or "hyperalgesia" has become a defined target of treatment protocols, and one possible mediator is felt to be the neurotransmitter serotonin (37,54–56). The same serotonin transporter responsible for its reuptake in the central nervous system is expressed throughout the gut and enteric nervous system, which derive from the same embryonic cells. Gut enterochromaffin cells contain over 90% of the body's total serotonin (37,56). Enterochromaffin cells line the gut lumen and act as sensory transducers, releasing serotonin in response to increased intraluminal pressure or inflammation, generating subjective abdominal discomfort by stimulating 5-HT3 receptors on extrinsic vagal afferents, and influencing gut peristaltic activity via stimulation of intrinsic enteric afferents. Serotonin is also an important neurotransmitter in descending pain-modulating pathways from brain regions such as the dorsal raphe (57) and periaqueductal gray involved in "gating" sensory information from the dorsal horn of the spinal cord (58).

Pain is thought to be a signal of a potential threat to physical integrity, and is accompanied by a wish to avoid additional distress. Abdominal pain can thus be viewed as a signal of threat to the organism (e.g., "bad food") that can generate an adaptive response (e.g., vomiting, increased motility); (56). Visceral afferents from the gut converge on the pontine parabrachial nucleus, ultimately projecting to brain regions important in mediating anxiety, fear, and emotional responses such as the amygdala (59). This raises the question of whether FAP and emotional disorders may share common pathophysiologic mechanisms. Interestingly, a common polymorphism regulating the transcription of the gene coding for the serotonin transporter has been associated with the response to the 5-HT3 receptor antagonist alosetron in adults with irritable bowel syndrome (60) and with the response of depressed adults to antidepressant medication. The same polymorphism is associated with greater activation of the amygdala in response to emotional stimuli (61) and with temperamental anxiety traits (62,63). Emotions have been characterized as brain states associated with the perception of rewards or punishments that generate bodily responses critical to survival, while feelings (awareness of emotion) are secondary and are mediated by different brain regions (64). It seems clear that both pain and anxiety can serve defensive neurobehavioral functions, steering the organism away from perceived threats and motivating adaptive behaviors. By analogy, the visceral hypersensitivity of FAP results in pain that is inappropriate to the context, just as an anxiety disorder is characterized by fear inappropriate to context.

While there is not a strong empirical base supporting a single approach to intervention, affected children and their families deserve to be educated about FAP and encouraged to ask questions. Understanding relationship between gut and brain and the potential role of visceral hyperalgesia

and serotonin in the pathogenesis of FAP may by useful to families. Reassurance about the absence of serious physical disease makes good sense. The patient and family should understand that the child's pain is real yet is not a signal of tissue damage. The importance of a therapeutic partnership or alliance should be discussed with the patient and the family, and areas of disagreement should be identified and brought into the open. The roles and responsibilities of the patient, the family, and the professional should be delineated, with an emphasis on complementary roles and responsibilities, and on clear communication. A regular schedule, healthy diet, adequate but not excessive sleep, and moderate, regular exercise are sensible suggestions. The use of deception (placebo or sham interventions) should be discouraged for reasons of ethics and credibility. An approach to the pediatric patient with medically unexplained physical symptoms is described in more detail elsewhere (65).

Because FAP tends to be chronic, waxing and waning, a quick cure by any therapy is unlikely. It is often counterproductive to cultivate the expectation of symptomatic "cure". A rehabilitative approach that treats FAP as a challenge to be overcome helps reframe the problem from one of finding a cure to one of coping successfully with a distressing problem. Active, problem focused approaches to coping are superior to passive acceptance, which is associated with greater symptom burden and functional impairment (66). Improvement should be understood as a personal success due to individual courage and hard work. Rather than focusing on pain as an excuse for school absenteeism, the child should be encouraged to attend and rewarded for the accomplishment with praise. Homebound instruction and prolonged school absenteeism should be avoided or challenged.

AN APPROACH TO INTERVENTION

Treatment choice should involve the informed opinions of patients and families. Offering the patient a trial of cognitive behavioral therapy or one of the self management strategies such as relaxation, biofeedback, or self-hypnosis within the framework of a rehabilitative approach is a reasonable place to start. Many families will nevertheless prefer a medication trial. We feel it is reasonable to reserve pharmacologic interventions for patients who fail conservative management or are unwilling to consider it. Despite the recent increase in popularity of TCAs among some clinicians, it is difficult to suggest such an approach given the potential for toxicity. There have been reports of sudden death in young children taking these medications, and there is an uninspiring record of performance of TCAs in the treatment of pediatric emotional disorders, particularly depression (49). We are currently examining the safety and efficacy of citalopram as a treatment for pediatric FAP in a double blind placebo controlled trial. Our past uncontrolled clinical approach has been to initiate treatment with an SSRI at low dose (citalopram or fluoxetine 10 mg per day), increasing to a potentially therapeutic dose over the next week (20 mg per day), and advancing to higher doses at approximately week four in the absence of full improvement (40 mg per day). Clinicians considering the use of SSRIs should understand that this is an off-label use of the medications and should review the potential risks and benefits with patients and families in detail, including the recent "black box warning" that antidepressant use can be associated with suicidal thinking and/or behavior in a small proportion of children and adolescents during the early phases of treatment. The United States Food and Drug Administration recommends that ideal follow up and safety monitoring take place weekly for the first month of treatment, then every other week in the second month, then at 12 weeks, with subsequent follow up taking place as appears clinically indicated.

Our clinical experience also suggests that some patients with FAP associated with emotional arousal and anxiety may benefit from a short course of a benzodiazepine such as clonazepam or lorazepam. Benzodiazepines can provide relatively rapid relief of anxiety, and thus have the potential of reassuring the patient and family and providing an example of how emotional activation and physical distress may be associated with FAP (65).

NEED FOR RESEARCH

There is no doubt that additional research is needed. A placebo control group is now considered essential in clinical trials for FGIDs (67). Spontaneous remission may occur in 30 to 40% of children with functional abdominal pain (3), and placebo response rates between 40 and 50% have been reported in studies of irritable bowel in children (9) and adults (32,48). Randomized double-blind placebo controlled design is required for drug trials of FAP given the lack of scientifically proven interventions in childhood, the need for assay sensitivity (i.e., ability to distinguish more efficacious from less efficacious treatments), the need to compare adverse drug effects to those occurring during placebo treatment.

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