World Journal of Gastrointestinal Pharmacology and Therapeutics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4292/wjgpt.v6.i4.96

World J Gastrointest Pharmacol Ther 2015 November 6; 6(4): 96-104
ISSN 2150-5349 (online)

EDITORIAL

Present state and future challenges in pediatric abdominal pain therapeutics research: Looking beyond the forest

Craig A Friesen, Jennifer V Schurman, Susan M Abdel-Rahman

Craig A Friesen, Division of Gastroenterology, Hepatology, and Nutrition, Children's Mercy Kansas City, Kansas City, MO 64108, United States

Jennifer V Schurman, Division of Developmental and Behavioral Sciences, Children's Mercy Kansas City, Kansas City, MO 64108, United States

Susan M Abdel-Rahman, Division of Pediatric Pharmacology, Medical Toxicology, and Therapeutic Innovation, Children's Mercy Kansas City, Kansas City, MO 64108, United States

Author contributions: All authors contributed equally to the content, writing, and revision of this manuscript; all authors had approved the final version of the manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest.

Correspondence to: Craig A Friesen, MD, Division of Gastroenterology, Hepatology, and Nutrition, Children's Mercy Kansas City, 2401 Gillham Road, Kansas City, MO 64108, United States. cfriesen@cmh.edu
Telephone: +1-816-2343016
Fax: +1-816-8021465

Received: May 4, 2015
Peer-review started: May 6, 2015
First decision: July 10, 2015
Revised: August 8, 2015
Accepted: August 20, 2015
Article in press: August 21, 2015
Published online: November 6, 2015

Abstract

At the present time, it is nearly impossible to treat pediatric functional gastrointestinal disorders associated with pain in an evidence based fashion. This is due to the overall lack of controlled studies and, even more importantly, the complexity of the contributors to disease phenotype which are not controlled or accounted for in most therapeutic trials. In this manuscript, we review the challenges of defining entry criteria, controlling for the large number of biopsychosocial factors which may effect outcomes, and understanding pharmacokinetic and pharmacodynamic factors when designing therapeutic trials for abdominal pain in children. We also review the current state of pediatric abdominal pain therapeutics and discuss trial design considerations as we move forward.

Key words: Pharmacogenomics; Functional dyspepsia; Abdominal pain; Irritable bowel syndrome; Therapeutic trials; Pharmacokinetics

Core tip: For abdominal pain therapeutics research to fulfill the promise of personalized medicine, there is a need to standardize trial entry criteria including validating Rome criteria as predictors of response. There is also a need to embrace complexity and recognize and control for the large number of biologic, psychologic, social, and pharmacologic factors which define each patient and may affect drug response. This approach will allow us not only to understand what treatments work for the population at large, but for the individual patient in front of us.

Friesen CA, Schurman JV, Abdel-Rahman SM. Present state and future challenges in pediatric abdominal pain therapeutics research: Looking beyond the forest. *World J Gastrointest*

Pharmacol Ther 2015; 6(4): 96-104 Available from: URL: http://www.wjgnet.com/2150-5349/full/v6/i4/96.htm DOI: http://dx.doi.org/10.4292/wjgpt.v6.i4.96

TEXT

Personalized medicine involves tailoring treatment to the specific characteristics, needs, and preferences of the individual patient[1]. At its heart, it's the "right drug at the right dose at the right time"[2]. The personalized medicine movement is primarily predicated on two things: (1) that an evidence base exists to support certain treatment options at the level of the population; and (2) that individual variation in patient characteristics, needs, and preferences can be identified in such a way as to allow evidence-based treatment to be optimally tailored. In a sense, personalized medicine focuses on the individual patient within the context of the population. While this is ideal, combining the best of evidence-based research with the best of clinical application, this is not the current reality for many conditions, including pediatric functional gastrointestinal disorders (FGIDs) associated with pain.

At the present time, it is nearly impossible to treat pediatric FGIDs associated with pain in an evidence based fashion. This is due to the overall lack of controlled studies and, even more importantly, the complexity of the contributors to disease phenotype which are not controlled or accounted for in most therapeutic trials. Each patient has a unique set of characteristics which must be understood when delivering an intervention. However, our individual patient care is largely informed by aggregate group data. Furthermore, studies are generally designed to minimize variation within the sample and thus may bear little relationship to actual patients seen in the clinical setting[3]. Group-wise analyses disguise substantial individual variation relevant to treatment. In short, we are unable to see the trees for the forest.

Diagnostic challenges also contribute to the familiar problems experienced by academic investigators and drug developers who conduct drug studies of FGIDs[4,5]. Principal among these are poorly understood etiologies for this very heterogenous group of conditions, poor diagnostic agreement in the classification of patients, incompletely validated criteria on which to subtype patients, and the fluctuating nature of symptoms[6-8]. Absent a clear understanding of the physiological, psychological, and behavioral elements that define this condition and reliable biomarkers that can facilitate patient subtyping[9,10], studies will invariably introduce uncertainty in their findings by pooling patients with putatively different underlying mechanisms of disease.

Collectively, these challenges lead to underpowered studies with variable response rates, large placebo effects, and limited relevance to the average pediatric patient with abdominal pain that is encountered in clinical practice. The role of this editorial is to lay out the relevant history and present state of therapeutics in pediatric abdominal pain research, as well as to identify existing challenges that will need to be considered and addressed to move the field forward toward the personalized medicine ideal in the future.

ROME CRITERIA AS THE ENTRY CRITERIA FOR THERAPEUTIC TRIALS

In 1999, the pediatric Rome Ⅱ committee established the first diagnostic criteria for FGIDs in children. These criteria were consensus-based and modeled after previous work (Rome Ⅰ) in adults. In 2006, the pediatric criteria were revised by the Rome Ⅲ committee. The Rome criteria define four FGIDs related to abdominal pain in children: Functional dyspepsia, irritable bowel syndrome, abdominal migraine, and childhood functional abdominal pain/syndrome[11] (Table 1). The majority of children and adolescents with chronic abdominal pain or discomfort meet criteria for an FGID[12,13]. At present, these Rome diagnoses form the entry criteria for nearly all pediatric abdominal pain therapeutic trials; however, the criteria have remained consensus-based and have never been completely validated nor shown to predict treatment response in clinical trials.

Utilizing the criteria in clinical practice or therapeutic trials is associated with some significant obstacles, including inherent ambiguity, inconsistent application, and differences in symptom reports between the patient and their parents or care givers. Although they seem to be "face valid", the Rome criteria lack a necessary degree of precision that translates to confusion on the part of patients, parents, and providers. For example, what is discomfort? Does the word discomfort mean nausea, bloating, or something else? Does it mean the same thing to parents as to the child? Do symptoms associated with discomfort result from different pathophysiologic processes or respond differently to treatments than does overt pain? In another example, an important criterion used to differentiate FD from IBS in the Rome criteria is relief with defecation which was defined in IBS as greater than 25% of the time but undefined in FD. Does having relief with a stool 5% or 10% of the time exclude FD? What happens when parents and children disagree about the percent time that defecation relieves pain? These are two relatively straightforward examples, but the criteria are open to interpretation in many areas. As suggested in the above examples, variance also is created by who provides the history and in what fashion. Utilizing standardized questionnaires, there is only fair to moderate agreement in diagnosis between symptom reports obtained from the patient and those obtained from their parent or guardian[13,14]. Agreement is low between the evaluating physician and either the patient or parent[13,14]. Further, responses on a standardized questionnaire also have low agreement to a daily symptom diary[14]. Perhaps due to the ambiguity, criteria are inconsistently applied. It has been shown that

Table 1 Criteria for functional gastrointestinal disorders related to pain in children

Functional dyspepsia[1]
Must include all of the following
Persistent or recurrent pain or discomfort centered in the upper abdomen
Pain or discomfort not relieved by defecation or associated with onset of a change in stool frequency or form
Irritable bowel syndrome[1]
Must include all of the following
Abdominal pain or discomfort associated with 2 or more of the following at least 25% of the time
Improved by defecation
Onset associated with a change in stool frequency
Onset associated with a change in stool form
Abdominal migraine
Must include all of the following
Paroxysmal episodes of intense, acute periumbilical pain lasting at least one hour
Intervening periods of usual health lasting at least weeks
Pain interferes with normal activity
The pain is associated with at least two of the following
Anorexia
Nausea
Vomiting
Headache
Photophobia
Pallor
Criteria must be fulfilled at least two times in the preceeding 12 mo
Childhood functional abdominal pain[1]
Must include all of the following
Episodic or continuous abdominal pain
Does not meet criteria for another FGID
Childhood functional abdominal pain syndrome
Must include childhood FAP and at least 25% of the time with at least one of the following
Some loss of daily function
Additional somatic complaints such as headache, limb pain, or difficulty sleeping

All require that there be no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the symptoms. [1]Criteria fulfilled at least once per week for at least 12 mo. FGIDs: Functional gastrointestinal disorders; FAP: Functional abdominal pain.

pediatric gastroenterologists only have fair to moderate agreement regarding FGID diagnosis even when presented identical clinical vignettes[15]. This problem may not be strictly limited to the pediatric population either. In adult FD, which has more specifically defined criteria, adherence to Rome criteria for inclusion was found in only 54% of clinical research trials[16].

Another challenge to utilizing Rome criteria in practice is that there is heterogeneity within diagnoses. Pediatric criteria, unlike the adult Rome criteria, do not recognize subtypes within either FD or IBS. In adult FD, there are two recognized subtypes: (1) postprandial distress syndrome (PDS), characterized by postprandial fullness or early satiety; and (2) epigastric pain syndrome, characterized by epigastric pain or burning unrelated to meals. These are not recognized in the pediatric criteria, although there is some evidence that PDS is associated with increased mucosal mast cells, anxiety, and depression in pediatric FD[17]. These are associations which may affect therapeutic responses to a given treatment. Likewise, IBS in adults may present with primarily constipation, diarrhea, or alternating symptoms; these patterns also have been described in children/adolescents, but are not specified as subtypes within the Rome criteria[18]. Ostensibly pediatric patients with primarily constipation would respond differently to an agent that affects motility than a patient with primarily diarrhea.

There also may be overlap between FGIDs, or between FGIDs and other conditions such as chronic nausea, GERD, or bladder dysfunction, which may influence treatment response. Nausea has been reported to be a commonly associated symptom in children with chronic abdominal pain which spans FGIDs[19]. Nausea frequency is associated with poor school and social functioning, and also predicts social disability; thus, nausea may be a symptom that could affect therapeutic response independent of the FGID category. In adults, significant overlap has been reported between FD and IBS, with overlap associated with more severe symptoms and increased psychological dysfunction[20,21]. Significant overlap has also been reported between FD and IBS in children, although some investigators report no overlap[12,13]. This represents another area of variability in application of the Rome criteria, as some investigators diagnose FD/IBS overlap while other investigators default to IBS when symptoms of both are present.

Finally, the Rome FGIDs were meant to be positive diagnoses in that they do not require organic disease to be ruled out *per se*; however, the criteria contain the requirement that there be no inflammatory, anatomic, metabolic, or neoplastic process to explain the

symptoms. Pediatric gastroenterologists vary significantly in what testing they believe is necessary to rule out biochemical or structural causes of abdominal pain[22]. Additionally, it has also been shown that the Rome Ⅲ criteria are not specific enough to rule out organic diseases and that alarm symptoms do not differentiate between organic and non-organic disease[23]. Taken together, the above issues may at least partly explain why only 39% of pediatric gastroenterologists report using the Rome criteria in their clinical practice[22].

Ultimately, there is a need to fully validate the Rome criteria in children as well as evaluate which symptoms naturally cluster together as has been done in adult populations. Even more importantly, current diagnostic categories (or other symptom complexes) and symptom variability within a diagnostic category need to be assessed for their ability to predict treatment response.

IMPLICATIONS OF THE BIOPSYCHOSOCIAL MODEL

Beyond issues of diagnostic classification, the development of abdominal pain itself is now widely considered to be a complex process. Chronic abdominal pain is believed to arise through multiple pathways that include biological (physiological, genetics), psychological (emotional, behavioral), and social (relational, environmental) factors which interact with one another. Each of these factors may contribute to initiation or maintenance of pain, as well as frequency, duration, and intensity of pain and other related symptoms. Consequently, children may arrive at the same result through different pathways. In addition, the process is dynamic and different processes may contribute to symptoms generation to varying degrees at different time points.

Patients may arrive at the same symptom complex by very divergent pathophysiologic processes including dysmotility, visceral hypersensitivity, inflammation, and alteration of the microbiome. FD for example has been associated with visceral hypersensitivity, as well as a wide variety of electromechanical disturbances including disorders of gastric emptying and accommodation, gastric dysrhythmias, and antroduodenal dysmotility[24]. FD has also been associated with inflammation, specifically mast cell accumulation in the antrum and eosinophil accumulation in the duodenum[25]. Similarly, IBS may result from visceral hypersensitivity, motility disturbances, low grade inflammation, and/or an altered intestinal microbiome[26]. Psychologic disturbances frequently co-exist and interact with other pathophysiologic factors. In addition, each patient has an environment which may interact with other pathohysiologic mechanisms and affect disease presentation and response to therapy over time.

Psychological functioning can be a significant source of patient variability, which cuts across all FGIDs. Psychological measures demonstrate clustering in children with FGIDs related to abdominal pain. In one study, approximately half of pediatric patients ith FGIDs showed no significant emotional, behavioral, or social disturbances, while 35%-45% demonstrated elevations only in anxiety scores and the remaining 13% demonstrated broad-based psychological problems[27]. In another study, pediatric patients with FGIDs demonstrated distinct patterns of pain and adaptation, with adaptation affecting clinical outcome[28].

Lastly, pain is influenced by a number of other broad social and environmental factors including interpersonal relationships, the natural environment, diet, and sleep. While some of these triggers appear common across individuals, there is likely variability among individuals on others[29]. For example, some patients have clear associations between inflammation, pain and the pollen count. These patients may respond to a treatment regimen differently during a time of high pollen exposure as compared to low exposure or differently than individuals unaffected by the pollen count[30].

Ultimately, the complexity of pediatric abdominal pain, and FGIDs specifically, creates significant challenges in controlling for disease variables in therapeutic trials. To date, this issue has largely been addressed through restrictive eligibility criteria, to reduce variability, or "noise", on the front end. However, the biopsychosocial model suggests that we may need to embrace individual variability, rather than control for it, in order to move closer to the personalized medicine ideal. In practice, this means that more liberal inclusion criteria combined with use of alternative research designs and/or more advanced statistical modeling approaches may be needed to support advancement in knowledge and care. We must assess each participant as a complex biopsychosocial system to understand how that system (*i.e.*, the whole person) affects treatment outcome and how that system rearranges in response to a treatment. This offers the hope of being able to determine which factors within the system predict the treatment that would be most effective for an individual patient.

CLINICAL PHARMACOLOGY

Historically, the lack of adequate pediatric drug trials, in general, could be blamed on several factors: (1) questions surrounding the ethics of conducting drug studies in children; (2) concerns related to the disproportionate financial investment required to support studies in a population which comprises a relatively small market share; and (3) assertions that pediatric studies are logistically more complex than comparable adult studies. Fortunately, academicians and regulators have come to appreciate that routinely administering medications to children when they have not been evaluated in this population is not ethically defensible[31,32]. Subsequently, United States legislation has prompted a major push to evaluate drugs in children, shifting discussions from "if" these studies should be performed to "when" and "how" they should be conducted[33]. With the general debate out

of the way, well-intentioned investigators are revealing additional challenges nested in the conduct of pediatric drug studies for FGIDs. Published studies continue to suffer from problems that can be loosely characterized as pharmacokinetic, pharmacodynamic, and diagnostic in nature.

Inadequacies in dosing regimen selection are perhaps the most straightforward to address. Since most academic investigations reflect repurposing of approved drugs there exists, at a minimum, some pharmacokinetic data that can be used to guide dosing decisions. Physiologically-based pharmacokinetic modelling and simulation strategies which take into consideration known maturational changes in the anatomy and physiology of major organs of disposition can provide a reasonable starting point from which to base dose selection[34]. The caveat is that this approach requires some estimation of desired exposure targets which, when unknown, often reflect adult exposures that have demonstrated safety. Notably, there is evidence to suggest that a priori modelling predictions do not always reflect observed pharmacokinetic profiles[35], which is why modelling exercises should be followed by confirmatory pharmacokinetic studies in advance of, or concurrent with, outcome based trials.

Importantly, the paradigm of "one and done" with respect to pediatric pharmacokinetic studies may not be a realistic option in FGIDs where marked variability in the genetic constitution, co-morbidities, and co-administered medications abound. Each of these factors can alter the pharmacokinetic profile of the drug in question to a different extent. However, a number of strategies can be integrated into the design of pediatric drug trials to enhance our understanding of the dose-exposure-response profile for selected treatment regimens. These include classical pharmacokinetic sampling in a small subset of patients, sparse pharmacokinetic sampling over a broader range of patients coupled with population pharmacokinetic analyses, and scavenged pharmacokinetic sampling or opportunistic clinical sampling similarly employing population-based analytical approaches. Though the latter strategies offer less than robust pharmacokinetic parameter estimates, they are only minimally labor intensive (as compared to classical pharmacokinetic studies) and are increasingly being accepted by regulatory agencies[36,37].

Additional pharmacokinetic considerations surround reliable drug delivery. A troublesome consequence of the failure of big Pharma to integrate children early in the drug development process is the lack of age-appropriate dosage formulations[38]. If the only available formulation is a solid oral dosage form, titrating the dose for children of varying weights can be problematic. Consequently, clinical trial outcomes that are not examined in the context of the weight-adjusted dose each participant received may miss important relationships between dose and response[39]. One must also consider the extrapolation of the research findings to the clinical practice setting. Data from a subset of children capable of swallowing the solid oral dosage form is of mixed utility in a pediatric practice setting where extemporaneous compounding may be undertaken to accommodate the needs of younger patients. Extemporaneous manipulation of the drug must be anticipated and the consequence on its relative bioavailability carefully assessed. Without these data, the fate of the molecule in the patient will be unknown and the care of the child potentially compromised[38].

Pharmacodynamic challenges reflected in drug studies of pediatric FGIDs center around adequately capturing unbiased outcomes[6]. As the need for objective biomarkers of treatment response is self-evident, and the current challenges related to subjective outcome measures have been thoughtfully addressed by others[7,10,40], we only reference the problem here to suggest that guidance documents authored by the United States Food and Drug Administration may offer a reasonable starting point for discussions related to the design and utilization of instruments developed to collect patient reported outcomes (PRO)[41,42]. These documents discuss the Agency's views on the adequacy of PRO measurement tools in the context of their characteristics, conceptual framework, content validity, criterion validity, ability to detect change, and suitability in special populations (*e.g.*, children, cognitively impaired, nonverbal, non-native language speakers). They also discusses the integration of these tools into clinical trials including protocol design considerations and statistical considerations nested in the analysis of PRO data[41,42]. We recognize that pediatric labeling is not a forethought for many academicians when designing FGIDs trials but the guidance offers insight into how a body of individuals tasked with the responsibility for determining the efficacy and safety of medicines view these instruments.

Ultimately, drug pharmacokinetics and pharmacodynamics and how these interact with genetics and disease processes must be considered if we are to gain a firm understanding of how to treat individual patients. Once we have selected the right drug for the right patient, pharmacokinetics and pharmacodynamics will allow us to fullfil the last step in a personalized medicine approach, the right dose at the right time.

CURRENT STATE OF ABDOMINAL PAIN THERAPEUTICS

Therapeutic management strategies for the treatment of functional gastrointestinal disorders share a common limitation with the sizeable majority of drugs on the market; namely, insufficient clinical evidence for their use in children. A Cochrane review published in 2002, and updated in 2008, identified a mere 6 trials evaluating drug-based interventions in children with recurrent abdominal pain or irritable bowel syndrome[4,43]. Importantly, only one-half of these trials were randomized and controlled. Our own more recent

Table 2 Chronological list of placebo controlled drug trials for functional gastrointestinal disorders related to abdominal pain in children and adolescents, including summary of treatment, sample size, and outcome

Ref.	Treatment	Diagnosis	Sample size (enrolled/completed)	Superior to placebo for pain relief
Symon and Russell[44] (1995)	Pitotifen	Abdominal migraine	16/14	Yes
Kline *et al*[45] (2001)	Enteric coated peppermint oil capsules	Irritable bowel syndrome	50/42	Yes
See *et al*[46] (2001)	Famotidine	Abdominal pain and dyspepsia	25/25	Yes
Friesen *et al*[47] (2004)	Montelukast	FD with duodenal eosinophilia	40/37	Yes
Bahar *et al*[48] (2008)	Amitriptyline	Irritable bowel syndrome	35/33	Yes
Sadeghian *et al*[49] (2008)	Cyproheptadine	Functional abdominal pain	36/28	Yes
Saps *et al*[50] (2009)	Amitriptyline	FD, irritable bowel syndrome, and functional abdominal pain	90/83	No
Pourmoghaddas *et al*[51] (2014)	Mebeverine	Functional abdominal pain	115/87	No

search of the literature revealed a total of 8 placebo-controlled drug trials for abdominal pain related FGIDs in children/adolescents, indicating that we have not made much progress in the past 7 years (see Table 2 for a summary)[44-51]. The clinical implication surrounding this paucity of well-controlled studies is limited empiric support for even basic prescribing decisions that clinicians make when managing pediatric patients with FGIDs.

Importantly, even within the existing literature, there are inconsistent findings that yield further confusion in applying results to clinical care. Comparison of the two separate trials of amitriptyline demonstrates some of the issues with regard to pediatric trials for FGIDs[48,50]; one trial demonstrated efficacy while the other did not. In adults, amitriptyline has been shown to be efficacious in those with diarrhea-predominant IBS[52]. One of the two pediatric trials for amitriptyline evaluated only participants with diarrhea-predominant IBS and demonstrated efficacy[48]. In contrast, the other pediatric trial evaluated both diarrhea- and constipation-predominant IBS patients, and also included patients with functional abdominal pain and FD, and did not demonstrate efficacy[50]. In addition to the much greater heterogeneity of the sample in the second study, there also was a trend for patients with IBS to be over-represented in the placebo group. The authors did analyze by specific FGID, but were likely underpowered to detect differences; descriptive statistics by group were not provided to allow the reader to evaluate effect size in this case. Thus, the lack of demonstrated efficacy for pain relief may have been due to patient selection, both in terms of inclusion criteria and randomization inequity. Another difference between the two studies may have been the dosing regimen. The per weight dosing likely varied significantly among patients within and across studies, although data on this was not presented nor analyzed as a covariate in the analysis. Furthermore, neither study determined amitriptyline concentrations in the blood to assess exposure. It is possible that success, or a lack thereof, was - at least in part - the result of differential dosing and/or exposure across patients.

Further, there have been almost no studies that have looked at layering of treatments. Although not the focus of this commentary, in addition to the drug trials noted above, there have been 6 controlled trials of probiotics, 4 controlled trials of fiber supplements, and a number of trials of a variety of psychological interventions (with various degrees of control), all mainly done in isolation of, or without regard for, other treatments. Layering of treatments is an important avenue to explore given the many potential contributors to symptoms in a given patient as previously discussed. It seems intuitive that identifying as many potential pain contributors in a given patient and addressing each simultaneously with a treatment specific to the contributor would be the most efficacious approach. However, this remains to be fully proven, as limited data exists. One example of existing evidence for layered treatment would be combining montelukast with biofeedback-assisted relaxation training (BART) in FD associated with duodenal eosinophilia. In the first study, montelukast was shown to be efficacious in this patient group in a double-blind, placebo-controlled crossover trial[47]. Then, in a second study, a separate group of patients was randomized to receive medication alone or in combination with BART. The combined, or layered, treatment resulted in more rapid resolution of pain and associated disability than seen for medication alone[52].

Finally, clinical trials for pediatric FGIDs have largely utilized traditional research designs that analyze data in the aggregate, which serves only to identify evidence at the level of the population without regard for individual characteristics, needs, or preferences. Specifically, within the drug trials identified by our group, only 3 utilized a cross-over design, only 1 evaluated potential biomarkers of response, only 1 utilized multivariate analysis of response predictors with anxiety as a co-variable, and only 1 assessed drug exposure utilizing pharmacokinetics. While there may be a role for

population-level evidence in creating a solid foundation from which individualization of treatment can occur, this cannot be the only approach if we are to learn how to effectively tailor those interventions for the benefit of our clinical patients.

WHERE DO WE GO FROM HERE?

First and foremost, we need to study drugs being used to treat abdominal pain in children. The approach must recognize that this is a multifactorial disease and that each patient has a unique biopsychosocial profile that may affect treatment response. The most direct way to account for this participant-to-participant variability is to have the participant serve as their own control, either through utilizing cross-over designs (when the intervention has limited durability) or through single subject designs. Ultimately, trials need to be of sufficient sample size and comprehensive in collecting data regarding biologic, psychologic, and social/environmental variables such that all of these potential factors can be assessed to determine individual characteristics or profiles that predict response. Trials, particularly early ones, also must consider pharmacokinetics and pharmacodynamics to assess relationships between drug dosing, drug exposure, and clinical response. Generalizability depends on controlling variables in the analysis rather than at entry through overly strict entry criteria.

Given our current state of understanding, investigations of medicines for abdominal pain may benefit from new approaches to trial design, including: (1) adaptive sample size re-estimation which can account for inaccurate assumptions of variance that can affect a studies power[53]; (2) enrichment designs that can limit the enrollment of participants with characteristics that may preclude the detection of a drug effect (*e.g.*, rapidly waxing and waning symptoms, non-adherence)[54]; and (3) n-of-1 trials which can better characterize individual treatment effects and potentially improve trial efficiency while reducing the necessary sample size[55]. Adaptive study designs involve prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of interim data. These designs allow the flexibility to alter the direction when it becomes clear that a particular intervention is effective such that a second treatment could be layered on. Conversely, these designs allow an intervention to be dropped when there is sufficient data to indicate that the treatment is ineffective. Single subject designs allow for fewer participants but require more frequent observation to ensure that change occurs only with the intervention. Such designs are more economical and allow researchers to tease out what specific treatments are most effective. These designs allow more rigorous study of combination treatments with different treatments phased in over time and also permit determination of the impact of dose escalation.

CONCLUSION

There can be value in preserving the traditional group aggregate approach, and there certainly remains room for the completion of high quality controlled clinical trials in the treatment of pediatric FGIDs. However, we also need to move past tradition to evaluate naturally occurring variation to understand which characteristic or set of characteristics are relevant to outcome. Pragmatically, this means embracing individual variability rather than restricting it *via* stringent sample selection criteria. This means investigating that variability through pharmacokinetic work to better predict exposure and inform dosing in individual patients. This means creatively applying alternative designs to the execution rather than applying research methods that are comfortable or familiar. And, this means learning new analytic strategies or partnering with statisticians familiar with analysis of adaptive designs, small *n* trials, and/or approaches to modeling intraindividual variation. Ultimately, to move forward, we need to understand variability, not control it.

In short, people are complicated and children with chronic abdominal pain are no exception. If we fail to appreciate that complexity in our research designs, we will never really get useful information out of the trials that we do. We will see only the forest, but not the trees within it. While population-based data can provide a place to start and the broad context for treatment, personalized medicine requires going beyond this to take individual characteristics, needs, and preferences into account in providing treatment to an individual. Thinking flexibly in our research, with individual variability in mind, will allow us to not only assess which treatments are efficacious but equally important, to understand when and for whom the treatment works[3]. Then we can determine not only which treatments work for the population at large, but also - and more importantly - for the individual patient in front of us.

REFERENCES

1 **U.S. Department of Health and Human Services Food and Drug Administration**. Paving the way for personalized medicine 2013. Available from: URL: http://www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf

2 **Hamburg MA**, Collins FS. The path to personalized medicine. *N Engl J Med* 2010; **363**: 301-304 [PMID: 20551152 DOI: 10.1056/NEJMp1006304]

3 **Schurman JV**, Gayes LA. Commentary: Putting tools in context: how pediatric psychologists can leverage science to improve clinical care. *J Pediatr Psychol* 2014; **39**: 262-263 [PMID: 24443739 DOI: 10.1093/jpepsy/jst140]

4 **Huertas-Ceballos AA**, Logan S, Bennett C, Macarthur C. Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. *Cochrane Database Syst Rev* 2008; (**1**): CD003017 [DOI: 10.1002/14651858.CD003017.pub2]

5 **European Medicines Agency**. Guidelines on the evaluation of medicinal products for the treatment of irritable bowel syndrome (CPMP/EWP/785/97) 2014. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500173457.pdf

6 **Korterink JJ**, Rutten JM, Venmans L, Benninga MA, Tabbers MM. Pharmacologic treatment in pediatric functional abdominal pain disorders: a systematic review. *J Pediatr* 2015; **166**: 424-431. e6 [PMID: 25449223 DOI: 10/1016/j.peds.2014.09.067]

7 **Levy RL**, van Tilburg MA. Functional abdominal pain in childhood: background studies and recent research trends. *Pain Res Manag* 2012; **17**: 413-417 [PMID: 23248815]

8 **Yacob D**, Di Lorenzo C. Functional abdominal pain: all roads lead to Rome (criteria). *Pediatr Ann* 2009; **38**: 253-258 [PMID: 19476297]

9 **Whitfield KL**, Shulman RJ. Treatment options for functional gastrointestinal disorders: from empiric to complementary approaches. *Pediatr Ann* 2009; **38**: 288-290, 292-294 [PMID: 19476303]

10 **Miller LE**. Study design considerations for irritable bowel syndrome clinical trials. *Ann Gastroenterol* 2014; **27**: 338-345 [PMID: 25330749]

11 **Rasquin A**, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, Walker LS. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006; **130**: 1527-1537 [PMID: 16678566]

12 **Walker LS**, Lipani TA, Greene JW, Caines K, Stutts J, Polk DB, Caplan A, Rasquin-Weber A. Recurrent abdominal pain: symptom subtypes based on the Rome II Criteria for pediatric functional gastrointestinal disorders. *J Pediatr Gastroenterol Nutr* 2004; **38**: 187-191 [PMID: 14734882]

13 **Schurman JV**, Friesen CA, Danda CE, Andre L, Welchert E, Lavenbarg T, Cocjin JT, Hyman PE. Diagnosing functional abdominal pain with the Rome II criteria: parent, child, and clinician agreement. *J Pediatr Gastroenterol Nutr* 2005; **41**: 291-295 [PMID: 16131983]

14 **van Tilburg MA**, Squires M, Blois-Martin N, Leiby A, Langseder A. Test of the child/adolescent Rome III criteria: agreement with physician diagnosis and daily symptoms. *Neurogastroenterol Motil* 2013; **25**: 302-e246 [PMID: 23216900 DOI: 10.1111/nmo.12056]

15 **Chogle A**, Dhroove G, Sztainberg M, Di Lorenzo C, Saps M. How reliable are the Rome III criteria for the assessment of functional gastrointestinal disorders in children? *Am J Gastroenterol* 2010; **105**: 2697-2701 [PMID: 20808296 DOI: 10.1038/ajg.2010.350]

16 **Stanghellini V**, Cogliandro R. Review article: adherence to Rome criteria in therapeutic trials in functional dyspepsia. *Aliment Pharmacol Ther* 2014; **40**: 435-466 [PMID: 25056101 DOI: 10.1111/apt.12865]

17 **Schurman JV**, Singh M, Singh V, Neilan N, Friesen CA. Symptoms and subtypes in pediatric functional dyspepsia: relation to mucosal inflammation and psychological functioning. *J Pediatr Gastroenterol Nutr* 2010; **51**: 298-303 [PMID: 20479684 DOI: 10.1097/MPG.0b013e3181d1363c]

18 **Self MM**, Czyzewski DI, Chumpitazi BP, Weidler EM, Shulman RJ. Subtypes of irritable bowel syndrome in children and adolescents. *Clin Gastroenterol Hepatol* 2014; **12**: 1468-1473 [PMID: 24486406 DOI: 10.1016/j.cgh.2014.01.031]

19 **Kovacic K**, Williams S, Li BU, Chelimsky G, Miranda A. High prevalence of nausea in children with pain-associated functional gastrointestinal disorders: are Rome criteria applicable? *J Pediatr Gastroenterol Nutr* 2013; **57**: 311-315 [PMID: 23591912 DOI: 10.1097/MPG.0b013e3182964203]

20 **Suzuki H**, Hibi T. Overlap syndrome of functional dyspepsia and irritable bowel syndrome - are both diseases mutually exclusive? *J Neurogastroenterol Motil* 2011; **17**: 360-365 [PMID: 22148104 DOI: 10.5056/jnm.2011.17.4.360]

21 **Piacentino D**, Cantarini R, Alfonsi M, Badiali D, Pallotta N, Biondi M, Corazziari ES. Psychopathological features of irritable bowel syndrome patients with and without functional dyspepsia: a cross sectional study. *BMC Gastroenterol* 2011; **11**: 94 [PMID: 21871075 DOI: 10.1186/1471-230X-11-94]

22 **Schurman JV**, Hunter HL, Friesen CA. Conceptualization and treatment of chronic abdominal pain in pediatric gastroenterology practice. *J Pediatr Gastroenterol Nutr* 2010; **50**: 32-37 [PMID: 19915496 DOI: 10.1097/MPG.0b013e3181ae3610]

23 **Gijsbers CF**, Benninga MA, Schweizer JJ, Kneepkens CM, Vergouwe Y, Büller HA. Validation of the Rome III criteria and alarm symptoms for recurrent abdominal pain in children. *J Pediatr Gastroenterol Nutr* 2014; **58**: 779-785 [PMID: 24866784 DOI: 10.1097/MPG.0000000000000319]

24 **Rosen JM**, Cocjin JT, Schurman JV, Colombo JM, Friesen CA. Visceral hypersensitivity and electromechanical dysfunction as therapeutic targets in pediatric functional dyspepsia. *World J Gastrointest Pharmacol Ther* 2014; **5**: 122-138 [PMID: 25133041 DOI: 10.4292/wjgpt.v5.i3.122]

25 **Friesen CA**, Schurman JV, Colombo JM, Abdel-Rahman SM. Eosinophils and mast cells as therapeutic targets in pediatric functional dyspepsia. *World J Gastrointest Pharmacol Ther* 2013; **4**: 86-96 [PMID: 24199024 DOI: 10.4292/wjgpt.v4.i4.86]

26 **Lee YJ**, Park KS. Irritable bowel syndrome: emerging paradigm in pathophysiology. *World J Gastroenterol* 2014; **20**: 2456-2469 [PMID: 24627583 DOI: 10.3748/wjg.v20.i10.2456]

27 **Schurman JV**, Danda CE, Friesen CA, Hyman PE, Simon SD, Cocjin JT. Variations in psychological profile among children with recurrent abdominal pain. *J Clin Psychol Med Settings* 2008; **15**: 241-251 [PMID: 19104969 DOI: 10.1007/s10880-008-9120-0]

28 **Walker LS**, Sherman AL, Bruehl S, Garber J, Smith CA. Functional abdominal pain patient subtypes in childhood predict functional gastrointestinal disorders with chronic pain and psychiatric comorbidities in adolescence and adulthood. *Pain* 2012; **153**: 1798-1806 [PMID: 22721910 DOI: 10.1016/j.pain.2012.03.026]

29 **Schurman JV**, Friesen CA. Identifying potential pediatric chronic abdominal pain triggers using ecological momentary assessment. *Clin Practice Pediatric Psychol* 2015 [DOI: 10.1037/cppp0000095]

30 **Magnusson J**, Lin XP, Dahlman-Höglund A, Hanson L LA, Telemo E, Magnusson O, Bengtsson U, Ahlstedt S. Seasonal intestinal inflammation in patients with birch pollen allergy. *J Allergy Clin Immunol* 2003; **112**: 45-50 [PMID: 12847478]

31 **Shaddy RE**, Denne SC. Clinical report--guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 2010; **125**: 850-860 [PMID: 20351010 DOI: 10.1542/peds.2010-0082]

32 **Royal College of Paediatrics and Child Health (RCPCH) Ethics Advisory Committee**. Guidelines for the ethical conduct of medical research involving children. *Arch Dis Child* 2000; **82**: 117-182 [DOI: 10.1136/adc.82.2.177]

33 **Tolbert J**, Goldman JL, Kauffman RE, Abdel-Rahman SM. The creating hope act: what's old is new again. *Pediatr Health Med Ther* 2014; **5**: 49-57 [DOI: 10.2147/PHMT.S46069]

34 **Wagner J**, Abdel-Rahman SM. Pediatric pharmacokinetics. *Pediatr Rev* 2013; **34**: 258-269 [PMID: 23729775]

35 **Rodriguez W**, Selen A, Avant D, Chaurasia C, Crescenzi T, Gieser G, Di Giacinto J, Huang SM, Lee P, Mathis L, Murphy D, Murphy S, Roberts R, Sachs HC, Suarez S, Tandon V, Uppoor RS. Improving pediatric dosing through pediatric initiatives: what we have learned. *Pediatrics* 2008; **121**: 530-539 [PMID: 18310202 DOI: 10.1542/peds.2007-1529]

36 **U.S. Department of Health and Human Services Food and Drug Administration**, Center for Drug Evaluation and Research (CDER). General clinical pharmacology considerations for pediatric studies for drugs and biological products 2014. Available from: URL: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf

37 **U.S. Department of Health and Human Services Food and Drug Administration**, Center for Drug Evaluation and Research (CDER). Guidance for industry population pharmacokinetics. December, 2014

38 **Abdel-Rahman SM**, Reed MD, Wells TG, Kearns GL. Considerations in the rational design and conduct of phase I/II pediatric clinical trials: avoiding the problems and pitfalls. *Clin Pharmacol Ther* 2007; **81**: 483-494 [PMID: 17329988]

39 **Benjamin DK**, Smith PB, Jadhav P, Gobburu JV, Murphy MD, Hasselblad V, Baker-Smith C, Califf RM, Li JS. Pediatric antihypertensive trial failures: analysis of end points and dose range. *Hypertension* 2008; **51**: 834-840 [PMID: 18332283 DOI: 10.1161/HYPERTENSIONAHA.107.104950]

40 **Irvine EJ**, Whitehead WE, Chey WD, Matsueda K, Shaw M, Talley NJ, Veldhuyzen van Zanten SJ. Design of treatment trials for functional gastrointestinal disorders. *Gastroenterology* 2006; **130**: 1538-1551 [PMID: 16678567]

41 **U.S. Department of Health and Human Services Food and Drug Administration**, Center for Drug Evaluation and Research (CDER). Patient-reported outcome measures: Use in medical product development to support labeling claims 2009. Available from: URL: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

42 **U.S. Department of Health and Human Services Food and Drug Administration**, Center for Drug Evaluation and Research (CDER). Irritable bowel syndrome- clinical evaluation of drugs for treatment 2012. Available from: URL: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM205269.pdf

43 **Huertas-Ceballos A**, Logan S, Bennett C, Macarthur C. Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. *Cochrane Database Syst Rev* 2008; **1**: CD003017 [PMID: 18254013]

44 **Symon DN**, Russell G. Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. *Arch Dis Child* 1995; **72**: 48-50 [PMID: 7717738]

45 **Kline RM**, Kline JJ, Di Palma J GJ. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. *J Pediatr* 2001; **138**: 125-128 [PMID: 11148527]

46 **See MC**, Birnbaum AH, Schechter CB, Goldenberg MM, Benkov KJ. Double-blind, placebo-controlled trial of famotidine in children with abdominal pain and dyspepsia: global and quantitative assessment. *Dig Dis Sci* 2001; **46**: 985-992 [PMID: 11341669]

47 **Friesen CA**, Kearns GL, Andre L, Neustrom M, Roberts CC, Abdel-Rahman SM. Clinical efficacy and pharmacokinetics of montelukast in dyspeptic children with duodenal eosinophilia. *J Pediatr Gastroenterol Nutr* 2004; **38**: 343-351 [PMID: 15076638]

48 **Bahar RJ**, Collins BS, Steinmetz B, Ament ME. Double-blind placebo-controlled trial of amitriptyline for the treatment of irritable bowel syndrome in adolescents. *J Pediatr* 2008; **152**: 685-689 [PMID: 18410774 DOI: 10.1016/j.jpeds]

49 **Sadeghian M**, Farahmand F, Fallahi GH, Abbasi A. Cyproheptadine for the treatment of functional abdominal pain in childhood: a double-blinded randomized placebo-controlled trial. *Minerva Pediatr* 2008; **60**: 1367-1374 [PMID: 18971897]

50 **Saps M**, Youssef N, Miranda A, Nurko S, Hyman P, Cocjin J, Di Lorenzo C. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. *Gastroenterology* 2009; **137**: 1261-1269 [PMID: 19596010 DOI: 10.1053/j.gastro.2009.06.060]

51 **Pourmoghaddas Z**, Saneian H, Roohafza H, Gholamrezaei A. Mebeverine for pediatric functional abdominal pain: a randomized, placebo-controlled trial. *Biomed Res Int* 2014; **2014**: 191026 [PMID: 25089264 DOI: 10.1155/2014/191026]

52 **Schurman JV**, Wu YP, Grayson P, Friesen CA. A pilot study to assess the efficacy of biofeedback-assisted relaxation training as an adjunct treatment for pediatric functional dyspepsia associated with duodenal eosinophilia. *J Pediatr Psychol* 2010; **35**: 837-847 [PMID: 20185416 DOI: 10.1093/jpepsy/jsq010]

53 **Proschan MA**. Sample size re-estimation in clinical trials. *Biom J* 2009; **51**: 348-357 [PMID: 19358221]

54 **U.S. Department of Health and Human Services Food and Drug Administration**, Center for Drug Evaluation and Research (CDER). Enrichment strategies for clinical trials to support approval of human drugs and biological products 2012. Available from: URL: http://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm332181.pdf

55 **Willke RJ**, Zheng Z, Subedi P, Althin R, Mullins CD. From concepts, theory, and evidence of heterogeneity of treatment effects to methodological approaches: a primer. *BMC Med Res Methodol* 2012; **12**: 185 [PMID: 23234603 DOI: 10.1186/1471-2288-12-185]

P- Reviewer: Actis GC, Tsai HH **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com