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# Current Awareness and Tools Available for Stress-Induced IBS in Children

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# Current Awareness and Tools Available for Stress-Induced IBS in Children

By

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## LIST OF ABBREVIATIONS

5-HT - 5-hydroxytryptamine

ACTH - Adrenocorticotrophic Hormone

AP-FGID - Abdominal Pain associated Functional Abdominal Pain Disorders

ANS - Autonomic Nervous System

CBT - Cognitive Behavioral Therapy

CNS - Central Nervous System

CRH - Corticotrophin-releasing Hormone

DME - Drug Metabolizing Enzyme

EC - Enterochromaffin Cells

ENS - Enteric Nervous System

FAPD - Functional Abdominal Pain Disorders

HPA - Hypothalamic-Pituitary-Adrenal

IBS - Irritable Bowel Syndrome

IBS-C - Irritable Bowel Syndrome constipation dominant

IBS-D - Irritable Bowel Syndrome diarrhea dominant

IBS-M - Irritable Bowel Syndrome mixed stool type

IBS-U - Irritable Bowel Syndrome not classified by other IBS types

IRB – Institutional Review Board

PGx - Pharmacogenomics

RAP - Recurrent Abdominal Pain

SNP - Single Nucleotide Polymorphism

SNRI - Selective Norepinephrine Reuptake Inhibitors

SSRI - Selective Serotonin Reuptake Inhibitors

TCA -Tricyclic antidepressants

## ABSTRACT

**Introduction:** Irritable Bowel Syndrome (IBS) is a gastrointestinal (GI) disorder that affects 13-38% of children (4-17 years) worldwide. Early life stresses like trauma, family pressure, abuse, and parenting factors may alter the HPA axis leading to GI sensitivity. IBS symptoms can impact an individual's quality of life, affect school attendance, and can be emotionally and financially stressful for the caregivers. To date, there is no known cure for IBS. While antidepressants have shown some efficacy in treating moderate to severe IBS in adults, prescribing a universal antidepressant drug, especially to the pediatric population is challenging due to the variability in IBS symptoms, lack of available clinical data on antidepressant efficacy in children, and fear of adverse drug reactions. Parents/ caregivers are often unaware of the IBS triggers and may question a doctor's recommendation on the use of antidepressants for pediatric IBS. Moreover, due to the lack of any specific diagnostic tests for IBS, doctors may prescribe diverse lab and imaging tests to rule out any organic disease before concluding an IBS diagnosis. Currently, there may be a gap of knowledge in diagnosing and treating pediatric IBS between medical professionals and caregivers' understanding. The study aims to highlight the current awareness of IBS among caregivers worldwide and bridge the gap between challenges faced by medical professionals and caregivers during a child's IBS management. By understanding the overlooked part of IBS treatment, a targeted approach can be used to guarantee the effects of antidepressant use that would provide comfort to the caregivers to adhere to a long-term treatment plan.

**Methodology:** A cross-sectional, observational study via online surveys was conducted worldwide with 12 medical experts and 69 parents/caregivers of children between 4-17 years of age to determine current awareness of IBS, challenges with IBS management, and opinions on using pharmacogenomic testing in antidepressant prescriptions for IBS in children.

**Results:** Forty-seven caregivers of children aged 4-17 years (24 males, 23 females) completed the survey. Ten out of 47 respondents had a confirmed diagnosis for their child's IBS. Out of the remaining 37 respondents who have never been diagnosed with IBS, 22% reported two or more GI-related symptoms along with frequent complaints of abdominal pain. Statistically significant differences were found for anxiety issues ($p=0.0027$) and bloating/changing bowel habits ($p=0.001$) between IBS-positive and IBS-negative pediatric groups. One in 5 caregivers denied the antidepressant use due to its inefficacy while 67% of caregivers who utilized antidepressant treatment for their child's IBS did not see any improvement in abdominal pain with the use of a Selective Serotonin Reuptake Inhibitor (SSRI). Rejection of antidepressant use by the caregiver and non-adherence to a long-term treatment plan were the main challenges faced by medical providers in prescribing antidepressants for pediatric IBS. Lastly, >50% of parents and medical professionals were open to utilizing pharmacogenomic testing for a targeted therapy approach.

**Discussion: A**nxiety and changing bowel habits are present in IBS patients making the use of antidepressants as a part of the treatment regimen. However, due to a lack of awareness about the pathophysiology of IBS, caregivers are often reluctant to utilize this approach for their children. Moreover, there is not enough clinical evidence currently that can assure the caregiver about the safety and efficacy of the antidepressant for their child. Emotional stress and expectation of immediate relief by the caregiver during their child's IBS episode may contribute to frequent doctor visits and non-adherence to a long-term treatment plan. Multiple doctor visits also engage the caregiver to invest in the treatment costs and time involved in the diagnosis of IBS. It is noted that antidepressants have worked differently for different individuals. Most parents caring for a child with IBS experienced either worsening symptoms or inefficacy of the drug. Drug metabolizing enzymes (DMEs) play a crucial role in drug efficacy and safety. SSRIs (Prozac®,

Zoloft™) are approved by the FDA for pediatric use but have shown no improvement in IBS flareups. However, off-label use of low-dose Tricyclic Antidepressants (TCA) in pediatrics is challenging due to their narrow therapeutic index. By checking for any polymorphisms in the respective DMEs, adequate choice and dosage of antidepressants can be predicted to minimize any adverse drug reactions thereby comforting caregivers and medical providers.

**Conclusion:** Thus, there is an urgent need to bring a pharmacogenomic intervention that can aid in accurate stress-induced IBS management, faster relief, and better adherence to the treatment regimen.

# CHAPTER 1: INTRODUCTION

Recurrent Abdominal Pain (RAP) is a primary concern observed in pediatric patients and represents a prevalent symptom of Functional Abdominal Pain Disorder (FAPD) (Rasquin et al., 2006; Vernon-Roberts et al., 2021, 2023). The symptoms of FAPD include abdominal pain, nausea, vomiting, regurgitation, diarrhea, or constipation. These symptoms arise due to diverse factors like genetic and psychosocial factors, alterations in gut motility and gut microbiota, and disturbances in central nervous processing thereby increasing visceral sensitivity and triggering immune response (Rexwinkel et al., 2022; Vernon-Roberts et al., 2021, 2023). There are four types of FAPDs namely functional dyspepsia, Irritable Bowel Syndrome (IBS), abdominal migraine, and functional abdominal pain-not otherwise specified (FAP-NOS) (Rexwinkel et al., 2022).

IBS is a chronic gastrointestinal condition characterized by RAP which is often accompanied by bloating, gas, diarrhea, and constipation. It is one of the most common subtypes of functional abdominal pain disorders (FAPD) prevalent in children and adolescents (Rexwinkel et al., 2022). Early life events, daily life stress, anxiety, and quality of life are known to be immediate triggers of IBS symptoms. During adolescence, a child goes through various stressful events including performance anxiety, family pressure, home environment, career decisions, mood disruptions, and identity recognition. All stressors can result in significant shifts in the HPA axis which may lead to anxiety, depression, hormonal imbalances as well a decrease in immune health (Romeo, 2013).

The symptoms of IBS vary among individuals and cannot be explained by any structural or biochemical abnormalities and can delay the correct diagnosis. The Rome Foundation is a non-profit organization of doctors and scientists who assist in diagnosing and treating disorders of the gut-brain axis like FAPDs. In 1989, the Rome Foundation developed a diagnostic criterion to classify functional pain abdominal disorders. This criterion is globally valid and has been revised

4 times since then (Hreinsson et al., 2023). The revisions in the current Rome IV criteria differentiate FAPDs in neonates (0-3 years) and older children/adolescents (4-18 years) (Baaleman et al., 2020; Koppen et al., 2017). According to the Rome IV criteria (2016), a child/adolescent is considered to have IBS if there are 4 or more episodes of RAP in a month and accompanied by two or more of the following symptoms: change in frequency of stool, change in the appearance of the stool, pain does not resolve with defecation and the symptoms cannot be explained by any other medical condition. Depending on the predominant form of stool type, IBS can be classified into 4 subcategories – IBS-C (constipation), IBS-D (diarrhea), IBS-M (mixed bowl habits), and IBS-U (unclassified) (Devanarayana & Rajindrajith, 2018; Lu et al., 2017; Saps et al., 2018).

### 1.1 Epidemiology of Irritable Bowel Syndrome (IBS)

IBS is a global epidemiological concern, impacting a range of 2% to 25% of children aged 4 to 17 years. Osemene, 2015 reported that IBS affects 10-15% of people worldwide out of which 13-38% are adolescents (Osemene, 2015). The epidemiology of IBS in children has been studied in different countries across the world. As per 2014 statistics, the prevalence of IBS as measured by Rome III criteria in Greece, Nigeria, South America, and Sri Lanka among children and adolescents is 2.9%, 9.9%, 3.8%-16%, and 3.6%-7% respectively. In China, the prevalence ranged from about 12-17% and Istanbul reported at about 22.6%. In comparison, the prevalence rate of IBS in children in the United States is lower (2-5%). IBS is more commonly seen in children between 8 to 12 years of age, particularly in girls (Devanarayana & Rajindrajith, 2018; Lu et al., 2017; Zhu et al., 2014).

## 1.2 The Interplay of Gut Microbiome & Stress in IBS

The gut-brain axis is a complex system of CNS & ANS, ENS, and neuroendocrine systems. The ENS, also called the second brain, is in the digestive tract wall. It has 5 times more neurons and ganglia compared to the spinal cord. An independent system regulates the bidirectional communication between the microbiome and the gut-brain axis (Singh et al., 2023). ANS transmits afferent signals received from the gut lumen to the CNS via enteric and vagus nerve terminals. Similarly, efferent signals are transmitted from the CNS to the gut wall. Neurotransmitters such as GABA, serotonin, melatonin, histamine, and acetylcholine are produced locally during this process (Appleton, 2018; Singh et al., 2023).

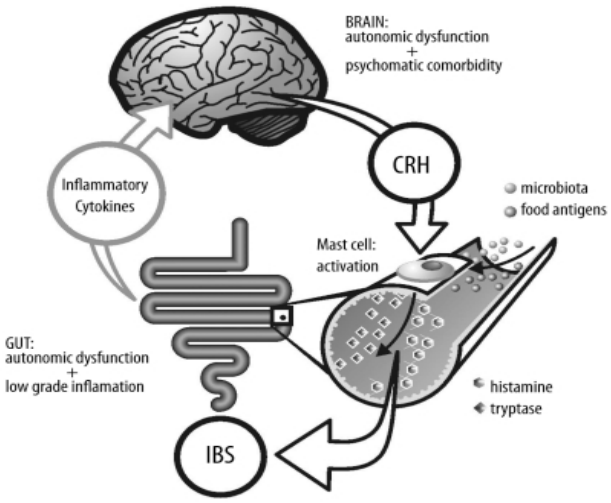


***Figure 1: The Gut-Brain Axis in IBS*** (Adapted from Philpott et al., 2011)

Figure 1 depicts how stressful triggers (efferent signal), inflammation, and infection (afferent signal) can activate the HPA axis that signals the release of corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), and cortisol (Devanarayana & Rajindrajith, 2018; Mayer et al., 2023; Philpott et al., 2011). The release of cortisol has a widespread effect on metabolism, hormones, and behavior and can result in disruption of the brain-gut homeostasis

causing increased intestinal motility, nutrient and gut microbiota imbalance as well as influence a person's mood (Karin et al., 2020; Qin et al., 2014).

Various neurotransmitters like serotonin (5-HT), somatostatin, cholecystokinin, and CRH are produced by the enterochromaffin cells (EC) and dendritic cells (DC) that help maintain microbiota and CNS homeostasis. The gut microbial populations are equipped with neurotransmitter receptors that can sense oligopeptides and monoamines that can impact their behavior and function. EC cells in the gut produce most of the body's serotonin and dopamine. This process is sensed by the gut microbiome via short-chain fatty acids (SCFA) which in turn promotes the synthesis of more 5-HT levels promoting GI motility, secretion, and immune responses. Gut microbiota plays a crucial role in regulating the HPA by 5-HT signaling and its dysbiosis can contribute to the pathophysiology of IBS (Mayer et al., 2023; Singh et al., 2023).

The gut microbiota is a community of diverse species that have evolved under different ecological systems over millions of years. *Lactobacillus* and *Bifidobacterium spp.* are the most prevalent gram-negative bacteria present in the gut microbiota along with other viruses, protozoa, and fungal species. These microorganisms survive in a symbiotic relationship in the gut by maintaining intestinal health and homeostasis (Cerdó et al., 2022; Singh et al., 2023). Their role is crucial in aiding digestion, vitamin synthesis, angiogenesis, and maturation of the host defense system. The mucosal surface is a delicate barrier that separates the gut microbiota from the host tissue thus protecting the human body from any immune response. Alterations in the gut microbiome (dysbiosis) have been identified to be closely associated with the pathology of various GI disorders including IBS (Craven et al., 2017; Singh et al., 2023).

It is well known that neuronal development and enhanced size of the microbiome are initiated at around 5 years of age and mainly configured by maternal gut microbiota (Hurley et al., 2019). In

2017, Palma et al. conducted a study that found that germ-free mice treated with microbiota from individuals with IBS-D displayed faster gastrointestinal transit, compromised intestinal barrier function, heightened innate immune response, and exhibited behaviors resembling anxiety, compared to mice receiving microbiota from healthy individuals suggesting the role of gut microbiome in GI pathologies (Palma et al., 2017).

Early life events, family stress, parenting factors, abuse, and several psychological factors including stress, anxiety, and depression, have been shown to cause IBS symptoms (Thapar et al., 2020). Many models have been discussed to understand the pathophysiology of IBS including the role of the immune, endocrine, and nervous system. Other studies have also highlighted food intolerance, intestinal injury and inflammation, bacterial overgrowth in the gut, and genetic transmission that could also induce IBS (Karin et al., 2020; Qin et al., 2014).

In a recent neurobiological model, various stressors directed at the central nervous system (CNS) are believed to cause alterations in the enteric nervous system (ENS) through the autonomic nervous system and hypothalamic-pituitary-adrenal axis (HPA axis). The alterations may lead to physiological changes in the gut causing visceral hypersensitivity, altered gut microbiota, mucosal permeability, malabsorption, and immune function. This is the top-down model. On the contrary, the bottom-up model suggests that stressors of the ENS including intestinal infections, mucosal inflammation, gut distension, food allergy, alterations in gut microbial flora, and increased intestinal permeability can disturb the CNS function through the sympathetic and vagal afferent systems thus altering neurotransmitter levels in the brain (Devanarayana & Rajindrajith, 2018; Mayer et al., 2023).

### 1.3 Current treatments for IBS

Clinical observations suggest that early-life adverse events and psychosocial stress have a crucial role in triggering IBS symptoms. Due to these observations, the most effective therapies for IBS include cognitive behavioral therapy (CBT), tricyclic antidepressants (TCA), and selective serotonin reuptake inhibitors (SSRIs). Other treatments like dietary interventions and probiotics, antispasmodics, herbal medications, acupuncture, etc. may be used alongside (Devanarayana & Rajindrajith, 2018; Mayer et al., 2023; Paul et al., 2013; Sandhu & Paul, 2014; Singh et al., 2023). However, these supplemental therapies may provide temporary relief (antispasmodics, antacids, laxatives, antidiarrheal agents, antiemnetic agents, etc), and may require an expert for diet planning, physical training, and performing interventions like CBT and hypnotherapy. Additionally, visits to specialists like dietitians, trainers, or a psychiatrist can be expensive and may require longer treatment times (Devanarayana & Rajindrajith, 2018; Donnet et al., 2022 Paul et al., 2013; Rexwinkel et al., 2022).

Antidepressants can be prescribed in cases of moderate to severe IBS where the child is missing school and feeling low due to anxiety. Depending on the IBS subtype, SSRIs for IBS-C; TCAs for IBS-D, and SNRIs for visceral pain may be utilized with other medications to restore normal brain-gut functioning (*Antidepressants for the Treatment of Functional Gastrointestinal Disorders*, n.d.). The antidepressants approved for adolescents by the FDA in the United States are Prozac® (fluoxetine) and Lexapro® (escitalopram). TCAs are not approved by the FDA for pediatric use. Some general practitioners may prescribe low-dose amitriptyline if the benefits weigh more than the harm (Dwyer & Bloch, 2019; Health, 2019).

### 1.4 Current Challenges with Pediatric IBS Management

According to the UNC Center for Functional GI & Motility Disorders, 67% of adolescent patients do not consult for IBS. Out of the remaining population who consult, they deny the role of stress in gastrointestinal disease and refuse to take any antidepressants. Moreover, parents make decisions for their children whether to give a certain medication. The black box warning on all antidepressants and the increased risk of suicidality often create hesitation among caregivers to use antidepressants for pediatric use (Bonilla & Nurko, 2018, Rasquin & Caplan, 2017). Additionally, the effects of antidepressants vary among individuals due to multiple factors like age, gender, physiological, environmental as well as genetic disposition. Genetic polymorphisms in drug-metabolizing enzymes (DMEs) genes that impact the pharmacokinetics or pharmacodynamics (PK/PD) of the antidepressants may cause varying exposures across multiple individuals taking the same dosage (Aka et al., 2017; Bondy, 2005; Bonilla & Nurko, 2018; Dwyer & Bloch, 2019; Lam et al., 2018; Lu et al., 2017).

Due to the unique relationship of the gut-brain axis, activation of the HPA axis can cause food intolerance due to visceral hypersensitivity; recurrent infections due to gut microbiota imbalance; and, psychological symptoms like anxiety and depression due to decreased 5-HT levels. The use of antidepressants has shown some efficacy in relieving IBS symptoms in adults. However, there is no clear evidence of the benefits of using antidepressants in children (Karunanayake et al., 2022). There are two main reasons why clinical trial data on the use of antidepressants in children is limited. First, a non-uniform study design and different primary endpoints across clinical trials conducted are not able to reproduce the results with increased variability among tested individuals. Second, due to severe adverse effects and black box warnings, caregivers are not willing to enroll

their children for any clinical trial that involves antidepressant use (Bondy, 2005; Bonilla & Nurko, 2018)

IBS can impact a child's quality of life leading to fear of flare-ups ultimately leading to missed school. The course of diagnosis and treatments expose them to unnecessary medications (antibiotics for stomach infections) and invasive diagnostic tests (endo/colonoscopy, blood tests). Lastly, chronic IBS episodes and their management add to stress among family members both emotionally and financially as a multi-specialist approach is required to rule out any missed diagnosis (Devanarayana & Rajindrajith, 2018; Koppen et al., 2017; Paul et al., 2013).

### 1.5 Classes of Antidepressants in IBS

Selective Serotonin Reuptake Inhibitors (SSRI), Serotonin Norepinephrine Reuptake Inhibitors (SNRI), and Tricyclic Antidepressants (TCA) are the three classes of antidepressants that can be used alongside other medications to relieve abdominal pain and psychological symptoms in children (Bonilla & Nurko, 2018).

1. *Selective Serotonin Reuptake Inhibitors (SSRI):*

SSRIs are the most prescribed antidepressants. In the U.S. FDA has approved the use of fluoxetine and escitalopram in pediatrics for the treatment of depression. SSRIs prevent the reuptake of serotonin by selectively inhibiting the presynaptic serotonin transporter. Increased levels of serotonin improve visceral hypersensitivity, enhance transit time, and reduce abdominal pain through its analgesic effect (Ajwah et al., 2020; Bonilla & Nurko, 2018). The DMEs involved in the metabolism of fluoxetine are *CYP2D6, CYP2C9, and CYP2C19* whereas escitalopram is metabolized by *CYP2C19 and CYP3A4* (Deodhar et al., 2021; X. Huang et al., 2021). Fluoxetine is generally considered the least binding profile to *SERT.* However, it is more specific than any

other TCA or MAO inhibitors. (Edinoff et al., 2021). Citalopram in two independent Randomized Clinical Trials (RCT) has shown improvement in IBS symptoms in children (4-18 years). No side effects were observed in the first 4 weeks. However, some children experienced mild drowsiness and dry mouth between 8 and 12 weeks of continued treatment (Bonilla & Nurko, 2018; Rexwinkel et al., 2021).

2. *Serotonin Norepinephrine Reuptake Inhibitors (SNRI):*

Duloxetine is the only approved SNRI for generalized anxiety disorders (GAD) for children aged between 7-17 years (Dwyer & Bloch, 2019). They work by inhibiting both serotonin (5-HT) and noradrenaline reuptake thereby increasing levels of both norepinephrine and serotonin (Bonilla & Nurko, 2018). Duloxetine is primarily metabolized by *CYP2D6* and *CYP1A2.* Polymorphisms in these genes can significantly impact drug efficacy and safety (Maciaszek et al., 2023).

3. *Tricyclic Antidepressants (TCA):*

TCA is the first line of antidepressants commonly used for major depressive disorders (MDD). Its use in children is not yet approved by the FDA. This class of antidepressants works by inhibiting serotonergic and/or noradrenergic pathways including histaminic, cholinergic, and alpha1-adrenergic receptor sites. Due to its mechanism of action, TCAs can help decrease GI motility in IBS-D patients, reduce abdominal cramps, and help maintain serotonin levels in the brain (Khalid & Waseem, 2023; Schoenfeld, 2023). Some studies including the ATLANTIS trial have shown the benefits of low-dose amitriptyline (10 – 30 mg) in adult IBS patients and is recommended as a second line of treatment (Ford et al., 2023). The treatment success with off-label use of amitriptyline in IBS pediatric patients is about 50% with reported side effects (headaches, fatigue, and dizziness) (Rexwinkel et al., 2021). A study conducted in 2011 with a small group of children

showed no significant improvement in pediatric IBS symptoms with amitriptyline. In another retrospective study with 98 children with AP-FGID, long-term treatment with amitriptyline (1-45 months) showed that 75% of children felt improvement in mood and IBS symptoms. Five percent of the tested population had adverse side effects and discontinued the treatment (Bonilla & Nurko, 2018). TCAs have a narrow therapeutic index, and, therefore, rates of hospitalization with its use are higher as compared with SSRIs (*Clinical Practice Guidelines: Tricyclic Antidepressant (TCA) Poisoning*, n.d., Khalid & Waseem, 2023). TCAs have a long elimination half-life (approx. 10-50 hours) and are highly protein-bound. Hence, an overdose of TCAs (10 – 20 mg/kg) can be potentially life-threatening as the absorption can be delayed due to its effect in decreasing GI motility. Some of the extreme adverse events of TCA overdose include suicidal ideation, heart block, and bradycardia (Bonilla & Nurko, 2018; Khalid & Waseem, 2023; Nassan et al., 2016). Amitriptyline is mainly metabolized by *CYP2D6 and CYP2C19*. Polymorphisms in these DMEs also contribute to varied dose responses and exposure to adverse events (Dean, 2017).

### 1.6 Sources of Variability in Antidepressant Treatment for Pediatric IBS

Interindividual variability in drug response is a common challenge faced by medical practitioners prescribing antidepressants to patients with anxiety and depression. Besides environmental, physiological, and psychological factors, genetics play an important role in determining the pharmacokinetic profile of a drug. Therefore, pharmacogenomics could be promising to patients to achieve the best efficacy and minimize adverse drug reactions (Radosavljevic et al., 2023).

The genetic makeup of an individual, particularly the genes responsible for drug-metabolizing enzymes (DMEs) and drug transport proteins, plays a pivotal role in shaping a drug's ADME profile. Variations in the CYP genotype can result in fluctuations in drug concentrations in the bloodstream, potentially leading to adverse drug reactions or impacting its effectiveness.

Individuals can be categorized as ultra-metabolizers (UM) if the drug is rapidly metabolized by DMEs, resulting in sub-therapeutic levels, or as poor metabolizers (PM) if CYP activity is compromised due to the loss of one or both genes, leading to supratherapeutic levels and adverse reactions. When DME genes function normally, individuals generally exhibit an extensive metabolizer (EM) phenotype. In some cases, the loss of one allele or reduced gene function results in an intermediate metabolizer (IM) phenotype. This variability in drug metabolism is a key factor contributing to the varying effects of antidepressants among individuals. (Pirmohamed, 2023; Radosavljevic et al., 2023).

### 1.7 The Concept of Pharmacogenomics

Pharmacogenomics (PGx) is the study of an individual's genetic makeup that can affect a drug's therapeutic response. PGx is a step closer to personalized medicine as it can explain interindividual differences in the response of the drug based on the unique genetic blueprint to help with dose prediction and prevent adverse events (Pirmohamed, 2023). The treatment of pediatric IBS is complex due to compounding interactions between psychological, and functional IBS subtypes and genetic variations in DMEs. The most common antidepressants for pediatric IBS are metabolized in the liver mainly by *CYP1A2, CYP3A4, CYP2D6, and CYP2C19* enzymes. Out of these, *CYP2D6* has over 100 allelic variants followed by *CYP2C19* with about 30 known genetic polymorphisms. The genetic diversity in DMEs can significantly impact the efficacy of antidepressants among individuals with IBS (Thümmler et al., 2018).

*Impact of Pharmacokinetic parameters on antidepressant safety and efficacy*

Depending on the single nucleotide polymorphism (SNPs), a person can be a poor metabolizer (both alleles are defective/deleted), ultra metabolizer (presence of multiple copies of a functional

gene), intermediate metabolizer (one allele is defective), and an extensive metabolizer (presence of a normal functional gene). Due to the presence of these polymorphisms, each patient would most likely respond differently to a single antidepressant (Austin-Zimmerman et al., 2021). Similarly, receptor binding is equally important for a drug to be efficacious. Any polymorphisms in the antidepressant target receptor would render the drug futile and lead to constant drug switching (Radosavljevic et al., 2023).

The table below summarizes how CYP450 and P-gp gene polymorphisms can impact the drug metabolism of various antidepressants and anti-anxiolytic medications (Radosavljevic et al., 2023).

**Table 1: Impact on antidepressant metabolism depending on DME polymorphisms** (Radosavljevic et al., 2023)**.**

| DME | Drug Class | Drugs | Polymorphisms | Metabolizer Type | Comments |
|---|---|---|---|---|---|
| ***CYP2D6*** | SSRI | paroxetine, fluvoxamine, and fluoxetine | CYP2D6*1, *2, *33, and *35 | EM | Normal function |
| | | | CYP2D6*9, *10, *14B, *17, *29, *41,*3, *4, *5, *6, *7, *11, *12, *14A, *36, and *68 | PM | Inc ADR (suicidal ideation) requires low doses |
| | SNRI | venlafaxine | CYP2D6 *6/*4, *5/*4, or *6/*6 | PM | Inc QT prolongation |
| ***CYP2C19*** | SSRI | escitalopram, citalopram, and sertraline | CYP2C19*1 | EM | Normal Function |
| | | | CYP2C19*17 | UM | Inc suicidal ideation |
| | | | CYP2C19*2 and *3 | IM/PM | Inc treatment |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | failure rate |
| ***CYP2C9*** | TCAs, and SSRIs | | CYP2C9*1 | EM | Normal function |
| | | | CYP2C9*2, *5, *8, and *11 (reduced function);<br>CYP2D9*3, *6, and *13 (loss of function); | IM/PM | - |
| ***CYP1A2*** | SSRI | escitalopram | rs2069521, rs4646425, and rs4646427 | PM | Inc side effects |
| | | paroxetine | rs4646425, rs2472304, and rs2470890 | UM | Slow response |
| ***P-gp/ MDR1*** | SSRI/ TCA | escitalopram, fluvoxamine, paroxetine, amitriptyline, and imipramine | MDR1/ABCB1 gene variants: G2677T (rs2032582) | | Increased brain penetration of drug |

*Impact of polymorphic variation on pharmacodynamic parameters*

Several antidepressants available on the market for the treatment of stress-induced IBS either inhibit serotonin or norepinephrine uptake or both to suppress depressive symptoms.

Serotonin transporter (*SERT)* is encoded by the *SLC6A4* gene and is responsible for serotonin reuptake from the pre-synaptic cleft. SSRIs specifically bind to the 5'-HTTLPR promoter regions to exert their effects. However, *SLC6A4* has 2 alleles – the short (S) and the long (L) allele. Patients with the S/S genotype have lower expression of serotonin transporters which causes reduced serotonin in the brain leading to depressive symptoms. Moreover, due to less active binding sites,

SSRIs cannot bind to the short allele and hence SSRIs are not effective. Therefore, switching to an SNRI or TCA would be more beneficial in this case. Similarly, polymorphisms in *SLC6A2* (Norepinephrine transporter - NET) or *SLC6A3* (Dopamine transporter – DAT) may influence a drug's mechanism of action (Lam et al., 2018; Radosavljevic et al., 2023; Taylor et al., 2010).

Despite the available information on genetic variation and its impact on the pharmacokinetic/pharmacodynamic (PK/PD) of a drug, genetic testing is rarely used in children and adolescent psychiatry. Gene polymorphisms in DMEs make it challenging for medical practitioners to decide on a particular dose and type of antidepressant. Most often, patients discontinue the treatment if they begin to see adverse effects or if the drug is ineffective. Constant drug switching often proves to be very frustrating for the individual due to the time and costs involved and often leads to discontinuation of the treatment (Jukic et al., 2022).

### 1.8 Study Objectives

The study aims to determine current awareness and treatments about pediatric IBS, challenges associated with treatment plans, and assess the confidence of healthcare professionals in choosing suitable antidepressants for pediatric IBS treatment through a survey-based questionnaire. The study also aspires to convey a message to healthcare providers, encouraging them to reevaluate the eligibility criteria for insurance policies and include provisions for pharmacogenomic testing coverage. By identifying and addressing gaps in the perspectives of caregivers and healthcare professionals on pediatric IBS treatment, it is possible to alleviate challenges faced by medical providers for the prescription of antidepressants for pediatric IBS. Additionally, incorporating genetic testing may better comfort the caregivers about the safety and efficacy of the antidepressant treatment thereby adhering to a long-term treatment plan for their child's IBS.

# CHAPTER 2: METHODOLOGY

## 2.1 Study Setting and Ethics Statement

A survey-based, cross-sectional, observational study was designed to emphasize the importance of pharmacogenomics in choosing antidepressants for the management of pediatric IBS worldwide. Two surveys (IRB #EXP452781) that were approved by the Harrisburg University Institutional Review Board (HU-IRB) were designed for caregivers/parents and medical providers to assess the prevalence and challenges associated with current IBS treatment. Before filling out self-administered questionnaires, all participants provided their written informed consent. The questions can be found in *Appendix I*.

## 2.2 Survey Modelling and Distribution

After approval from the HU-IRB, the surveys were modeled on the Qualtrics XM software which allowed us to administer the survey confidentially, in multiple languages as well as offer a broad internet distribution platform. The surveys were published on social media platforms (WhatsApp, Facebook, LinkedIn, Reddit, Twitter) and shared on the International Foundation for Gastrointestinal Disorders clinical trial page (https://iffgd.org/research/clinical-trials-and-studies/#ibs) through an anonymous link. QR codes were also posted in public places. The survey responses were collected for a period of 2 months from January 2024 to March 2024.

## 2.3 Participants

This study included responses from all caregivers caring for a child between 4-17 years of age and employed a voluntary sampling method and used it further to purposely sample only the IBS-positive patients (McCombes, 2023). Using the following formula, $n = pq/(d/t)^2 = t^2 \times pq/d^2$, where t = 1.96 (error of the first kind), p = 20% (estimated prevalence), q = 1 – p (80%), and d =

5% (margin of error) the expected minimal sample size for this study was 245 (Younas, 2019). Due to the anonymity of the survey, the study could not embed a tracker to calculate the response rates, and the response rate was calculated as (number of completed responses/total number of responses) *100. Based on the calculations, our response rate was 68% and hence the adjusted sample size required for this study was calculated to be 166. For the medical professionals' survey, we aimed to purposely select at least 10 responses from only pediatricians, general practitioners, and gastroenterologists to get an idea of their perspective.

### 2.4 Inclusion and Exclusion Criteria

To determine the prevalence and awareness about IBS among caregivers, the responses were considered only if the respondent cared for a child between 4-17 years of age. The inclusion criteria to understand the trends and challenges in current diagnosis and treatment for IBS, a caregiver must care for a child between 4-17 years of age and have a confirmed diagnosis of IBS by a healthcare provider. The opinions of healthcare professionals were considered only if they could diagnose and prescribe medications. A quality assurance question to ensure truthful responses was also included in both surveys and considered one of the criteria for inclusion of the data. The table below summarizes the inclusion and exclusion criteria based on the different goals of the study.

**Table 2: Summary of inclusion criteria based on the goal of the research for each survey.**

| Survey Type | Goal of the research | Inclusion criteria |
|---|---|---|
| Survey for caregivers | Awareness and Prevalence of Pediatric IBS | All parents/caregivers caring for a child between 4-17 years. |

| | | |
|---|---|---|
| | Current treatments and challenges associated with pediatric IBS and willingness of caregiver to utilize genetic testing. | Parents/caregivers caring for a child between 4-17 years AND who has been diagnosed with IBS by a healthcare professional. |
| Survey for medical providers | To determine experience in treating pediatric IBS (common age groups, symptoms, treatment plan, and its challenges) and willingness to utilize genetic testing for antidepressant choice. | Any healthcare professional with a basic medical degree AND who can prescribe medications. |

**2.5 Questionnaires:**

*2,5,1 Survey for Caregivers:*

Personal General Information: Personal data such as the age of the child, sex, and country of residence were included in the questionnaire.

Awareness & Prevalence of IBS: The respondents were asked about the frequency of their child complaining about stomach pain, anxiety issues, and changing bowel habits. The survey also asked if the child had a confirmed diagnosis of IBS. The Rome IV criteria was utilized to categorize

potential IBS patients who displayed 2 or more symptoms along with frequent complaints about abdominal pain but have never been diagnosed with IBS by a healthcare professional.

Treatment for Pediatric IBS: The survey incorporated questions to reflect on the diagnostic tests and treatments that each pediatric IBS patient underwent upon onset of GI symptoms.

Antidepressant Use & Experience: Caregivers were asked if they accepted the use of antidepressants if prescribed. The survey also asked questions regarding the benefits and challenges associated with antidepressant use during IBS treatment.

Caregiver Satisfaction with Treatment Plan and Availability of Support Resources: Questions to evaluate the frequency of follow-up appointments, reasons for treatment evaluation, and awareness of new developments for IBS treatment were asked.

Openness to Genetic Testing: Lastly, the survey gathered responses from parents/caregivers to assess the acceptance rate to utilize genetic testing for their child's personalized IBS treatment.

*2.5.2 Survey for Doctors (General Practitioners, Pediatricians, Gastroenterologists, Psychiatrists):*

General Information: Healthcare providers were asked to specify their medical specialty to determine the eligibility criteria.

Pediatric Diagnosis & Assessment: The survey incorporated questions to understand current methods used to determine pediatric IBS, common symptoms, the prevalence of anxiety/ depression with IBS, and the most affected age group among the pediatric population.

Severity of Depression with IBS: Doctors were asked to rate the severity of anxiety/depression symptoms on a scale of 0-5 (0= none & 5= severe) in pediatric IBS patients.

Treatment Approach: Doctors were asked about the treatment plan for pediatric IBS and their experience in prescribing antidepressants.

Antidepressant Selection & Dose Determination: Doctors were asked to select the most suitable antidepressant for pediatric IBS management and their selection criteria for choosing a particular antidepressant. They were also asked about challenges while prescribing an antidepressant to a pediatric IBS patient.

Openness to Genetic Testing: Lastly, the survey gathered responses to observe if the medical professionals were willing to utilize genetic testing for the choice and dosage of antidepressants for pediatric IBS treatment.

**2.6 Data Collection and Analysis**

After a period of 2 months (January 2024 to March 2024), the responses were exported from Qualtrics XM into an Excel file. The responses were screened for incompleteness, and quality assurance and filtered based on the inclusion and exclusion criteria (refer to Table #2). All responses that fulfilled the inclusion criteria were considered for statistical analysis using GraphPad Prism 9. Categorical variables were analyzed by Pearson's Chi-square ( $\chi^2$) test using GraphPad Prism 9 and P-values were calculated. The Chi-square test helped with approximating a sample size that is expected to be large in a worldwide sampling. A P-value of less than 0.05 was considered statistically significant (denoted by *).

## CHAPTER 3: RESULTS

A total of 69 caregivers/parents and 20 healthcare professionals were collected over a period of 2 months. We excluded responses from caregivers who did not care for a child aged between 4-17 years, had incomplete responses, or did not pass the quality control question. Similarly, responses from healthcare professionals who could not prescribe medications and/or had incomplete responses were excluded. After applying the exclusion criteria as described above, a total of 47 caregivers/parents caring for a child between 4-17 years (23 females, 24 males) and responses from 11 healthcare professionals were considered in the final analysis. General characteristics and observed symptoms as reported by the caregiver are summarized in Table 3.

**Table 3: General characteristics & observed symptoms of pediatric population with or without IBS n (%) [* denotes p-value < 0.05]**

| | Total (n=47) | IBS (n=10) | Non-IBS (n=37) | $\chi$ 2 | P-value |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| Male | 24 (51%) | 5 (50%) | 19 (51%) | 0.005 | 0.94 |
| Female | 23 (49%) | 5 (50%) | 18 (49%) | | |
| **Age Group (Years), Mean ± SD** | 11.5 ± 3.93 | 11.1 ± 3.38 | 11.6 ± 4.06 | | |
| 4-7 | 9 (19.1%) | 2 (20%) | 7 (18.9%) | | |
| 8-12 | 17 (36.1%) | 4 (40%) | 13 (35.1%) | 0.11 | 0.94 |
| 13-17 | 21 (44.6%) | 4 (40%) | 17 (45.9%) | | |
| **Stomach Pain** | | | | | |
| Always | 1 (2.1%) | 1 (10%) | - | | |
| Sometimes | 31 (65.9%) | 7 (70%) | 24 (64.8%) | 4.2 | 0.11 |
| Never | 15 (31.9%) | 2 (20%) | 13 (35.1%) | | |
| **Anxiety issues** | | | | | |
| Always | 3 (6.3%) | 3 (30%) | - | | |
| Sometimes | 19 (40.4%) | 3 (30%) | 16 (43.2%) | 11.86 | 0.0027* |
| Never | 25 (53.1%) | 4 (40%) | 21 (56.7%) | | |
| **Bloating/Changing Bowel Habits** | | | | | |
| Yes | 7 (14.8%) | 5 (50%) | 3 (8.1%) | | |
| No | 26 (55.3%) | 1 (10%) | 25 (67.5%) | 13.53 | 0.001* |
| Maybe | 13 (27.6%) | 4 (40%) | 9 (24.4%) | | |

Chi-square tests from each category suggested no significant difference in the prevalence of IBS based on gender and age in the pediatric population. However, the Chi-square and Exact Fisher t-

test showed significant p-values for anxiety (p=0.0027) and bloating/changing bowel movements (p=0.001) between IBS and non-IBS pediatric patients.

### 3.1 Current Awareness and Prevalence of Pediatric IBS

*3.1.1 Caregivers' Perspective*

Ten out of 47 parents reported a confirmed diagnosis of IBS by a healthcare professional in their child (Mean age 11.1 ± 3.39 [SD] years). Out of the 10 IBS-positive patients, 5 reported that they have been prescribed antidepressants for their child's IBS management. Their experiences and challenges were compared with the perspectives of medical professionals to bridge the gap in utilizing antidepressants in the management of IBS. Out of the 37 respondents whose children have never been diagnosed with IBS, 7 parents said that their child has only anxiety symptoms, 4 complained about frequent gas, 2 of them faced regular bloating issues, 2 had frequent changing bowel habits, 3 reported recurrent GI infections only, 3 reported stomach pain only, and the remaining 8 did not have any symptoms. 8 respondents complained of two or more symptoms of IBS including stomach pain, bloating, constipation, and anxiety (Mean age 10.7 ± 4.65 [SD] years). The results are summarized in Table 4.

**Table 4: Observed Symptoms of Non-IBS Pediatric Population**

| Symptoms | n |
|---|---|
| Anxiety only | 7 (18.9%) |
| Gas only | 4 (10.8%) |
| Bloating only | 2 (5.4%) |
| Changing Bowel habits only | 2 (5.4%) |
| Repeated GI infections only | 3 (8.1%) |
| Stomach Pain only | 3 (8.1%) |
| Stomach Pain + Any 2 IBS symptoms | 8 (21.2%) |
| No symptoms | 8 (21.2%) |

The results from the caregiver survey analyzed the prevalence of IBS, Non-IBS, and potentially IBS + across different countries. The results are summarized in figure 2.

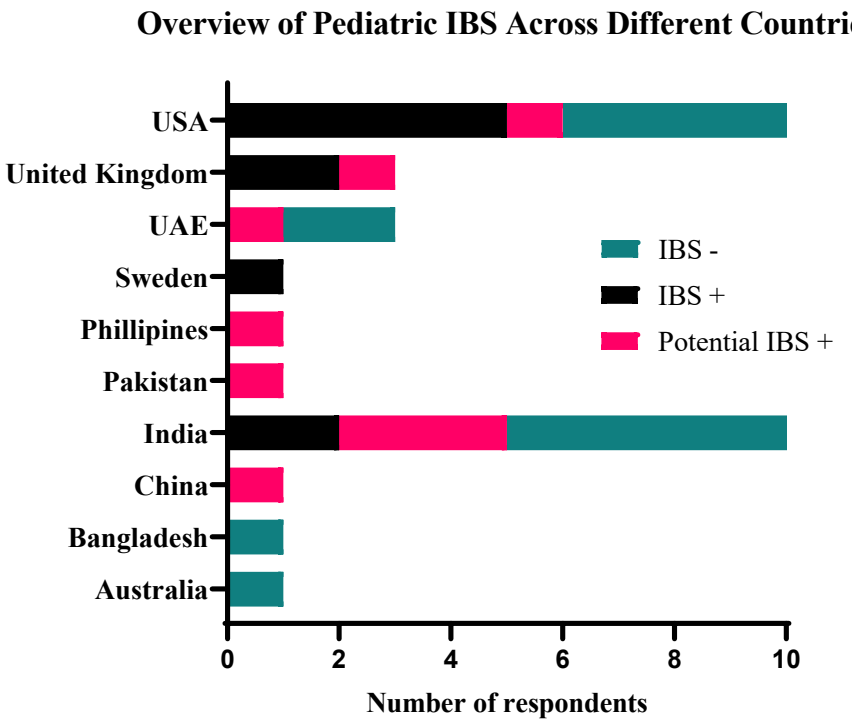


***Figure 2: Overview of pediatric IBS across different countries - Grouped bar chart showing confirmed cases of IBS vs potential IBS cases across different countries.***

*3.1.2 Medical Providers' Perspective*

Eleven medical professionals (4 Gastroenterologists, 6 General Practitioners, and 1 Psychiatrist) reported that IBS is most prevalent in the age group of 13-17 years with abdominal pain being the most common symptom. Eight out of 11 (72%) medical professionals have experienced anxiety/depression co-occurring with IBS symptoms in pediatric patients. The mean severity of depression on a scale of 0 to 5 was reported to be moderate (2.5 ± 0.76 SD). The survey suggested that four out of 11 (33%) medical professionals would prescribe antidepressants based on the

severity of symptoms, lack of response from other treatments, and co-occurrence of anxiety/depression symptoms.

### 3.2 Common Diagnostic Tests: A comparison of caregivers' experience vs medical recommendations

*3.2.1 Caregivers' Experience*

Each IBS-positive patient had a confirmed diagnosis of IBS by utilizing one or more diagnostic procedures. Rome IV criteria and blood tests (60%) were the most common diagnostic methods reported by caregivers for their child's IBS diagnosis (Figure 3a).

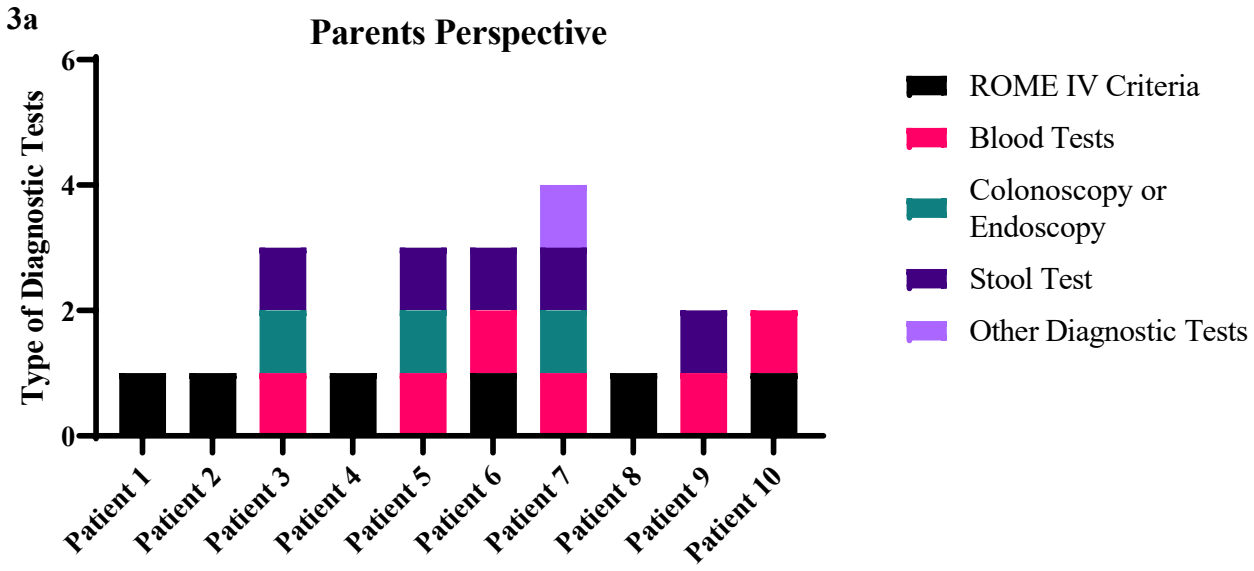


***Figure 3a: Parent's experience for diagnostic tests for pediatric IBS - Grouped bar chart showing type of diagnostic tests undergone by children (4-17 years) (n=10) for IBS diagnosis. Respondents selected all applicable choices for this question.***

*3.2.2 Choice of Diagnostic Tests Among Medical Professionals for Diagnosing Pediatric IBS*

The preference for each available diagnostic method for IBS diagnosis differed among general practitioners and gastroenterologists. The opinions of a psychiatrist and a psychologist were not considered as the initial diagnosis is through a primary care provider or a gastroenterologist. Based

on the survey data the diagnostic criteria to diagnose pediatric IBS by a gastroenterologist is solely through utilizing Rome IV criteria. On the other hand, a general practitioner would consider blood tests along with imaging technology like endoscopy or colonoscopy as depicted in Figure 3b.

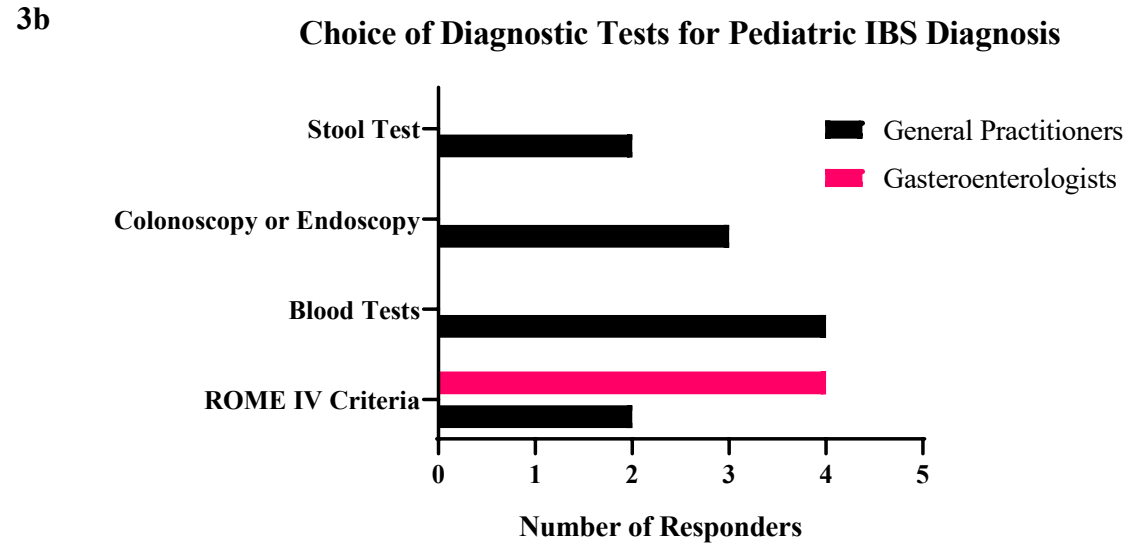


***Figure 3b: Choice of diagnostic tests among general practitioners and gastroenterologists - Bar chart showing difference in choice of diagnostic tests among general practitioners (n=6) and gastroenterologists (n=4) for pediatric IBS diagnosis. Respondents were able to select more than one choice.***

### 3.3 Common Treatments and Management Therapies: A comparison of caregivers' experience vs medical recommendations

The most common treatment method for pediatric IBS management as reported by caregivers of 10 IBS pediatric patients was dietary and lifestyle changes (60%) and/or medications like antispasmodics, antihistamines, and immune suppressants to combat stomach pain (50%). Depending on the severity of the symptoms, only 30% pediatric IBS patients underwent stress management therapies, 30% took antidepressants and 30% preferred complementary therapies (Figure 4a).

The pediatricians and gastroenterologists were asked to select all treatments that they would recommend for pediatric IBS management. Figure 4b summarizes the difference in the choice of

therapies for IBS management. While 40% of gastroenterologists would prefer to prescribe an antidepressant, 60% of general practitioners would recommend using complementary therapies like CBT and probiotics.

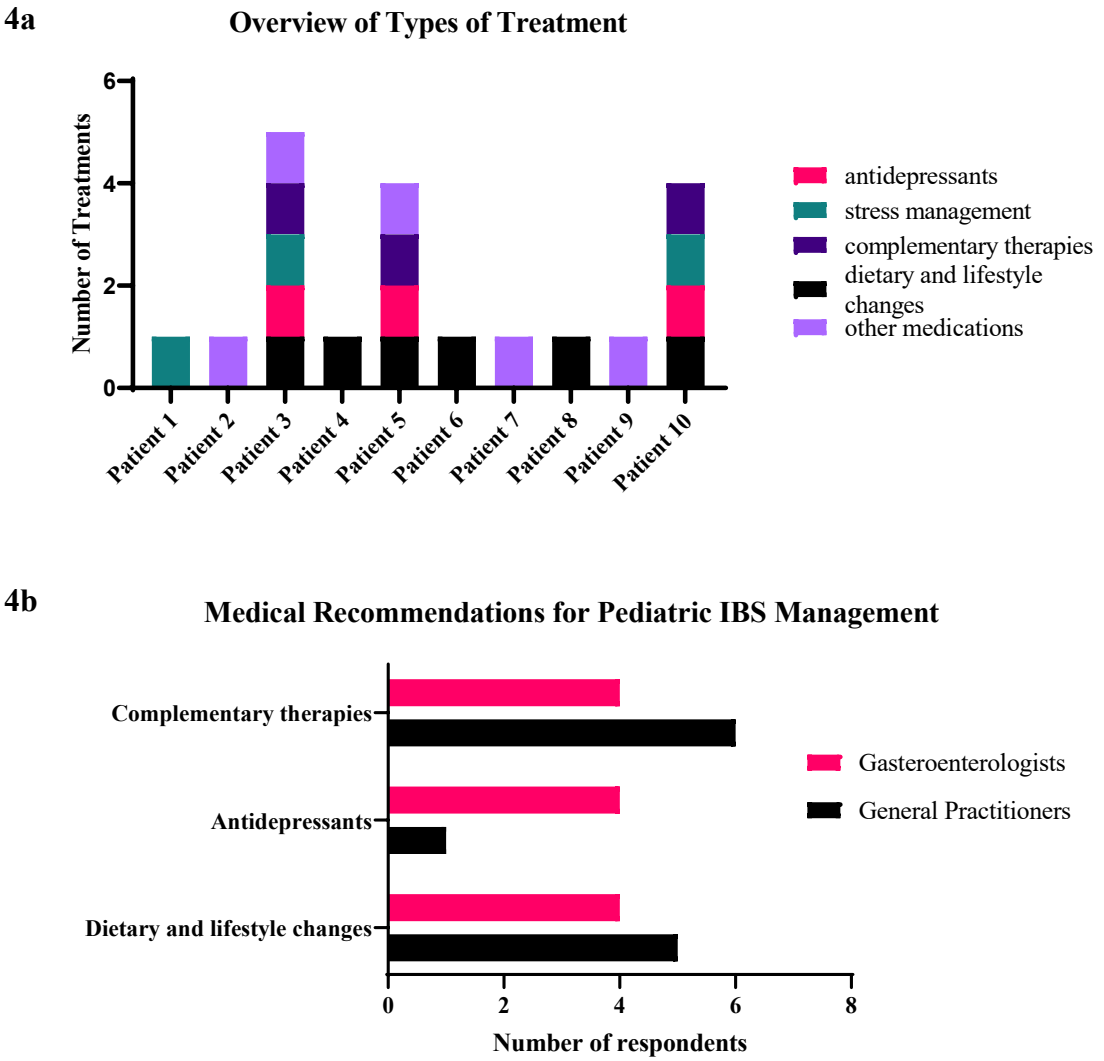


***Figure 4: IBS management therapies for pediatric IBS - Grouped bar chart showing (a) type of medical treatment undergone by each IBS patient (n=10) vs (b) recommended medical treatments by medical professionals (n=11). Respondents were able to select multiple choices.***

### 3.4 Antidepressant Prescriptions for IBS Management – Choice of Doctors vs Actual Prescription

Among 10 caregivers whose child had a confirmed diagnosis of IBS, only 5 were recommended antidepressant therapy. Four of the 5 caregivers agreed to use antidepressants (SSRIs-75%; TCA-25%) for the management of their child's IBS. One out of 5 caregivers (20%) denied antidepressant therapy due to the general thought of antidepressants being ineffective. Figure 5a shows the type of antidepressant used by pediatric IBS for the management of IBS symptoms.

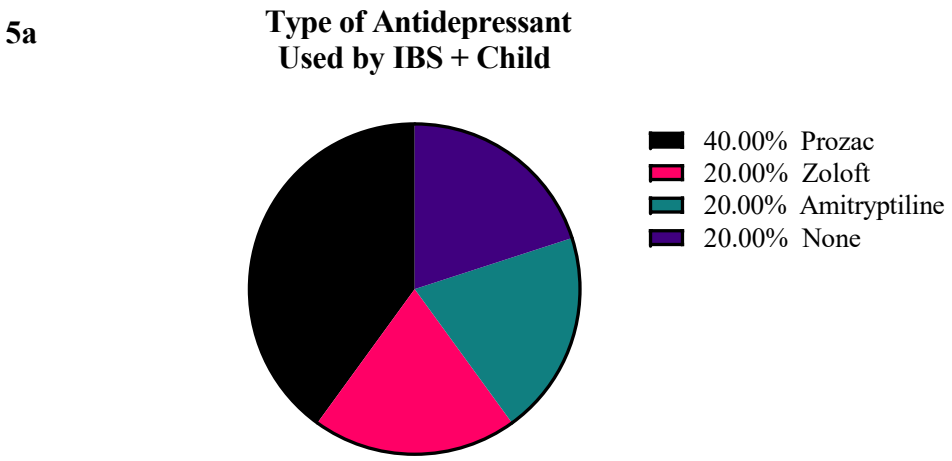


***Figure 5a: Type of antidepressants used by IBS+ pediatric patients - Pie chart representing different antidepressants (AD) used by children (4-17 years) (n=5) for IBS management.***

From a doctor's perspective, 45.4% of medical professionals recommended TCAs (amitriptyline) as the choice of drug for pediatric IBS management while only 27.2% preferred SSRI (Prozac, Lexapro) and 9% preferred benzodiazepine class of antidepressant for pediatric IBS management (Figure 5b).

5b

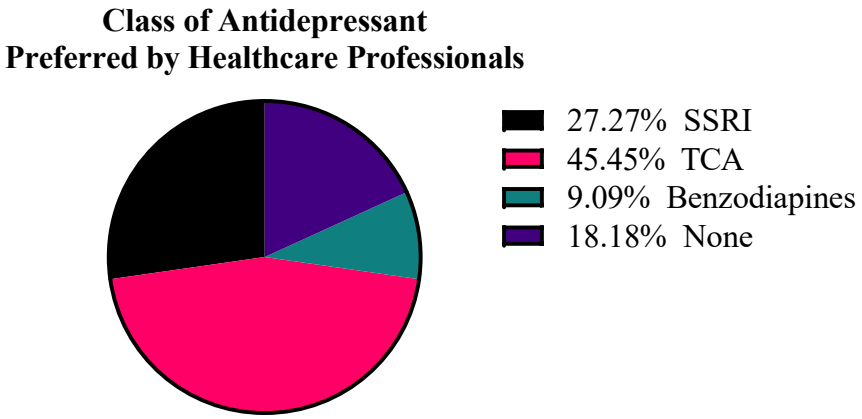


***Figure 5b: Choice of antidepressants by medical providers for pediatric IBS - Pie chart representing doctor's preference (n=11) of antidepressant (AD) choice for pediatric IBS management.***

### 3.5 Patient Patient-Observed Benefits of Antidepressant Use vs Challenges of Medical Professionals for Antidepressant Prescription for Pediatric IBS

Survey data shows that pediatric IBS patients who adhered to SSRI treatment observed improvement in mood, had better bowel movements, and reduced stress levels while patients taking amitriptyline had less frequent stomach pain and reduced anxiety/stress (Figure 6a).

6a

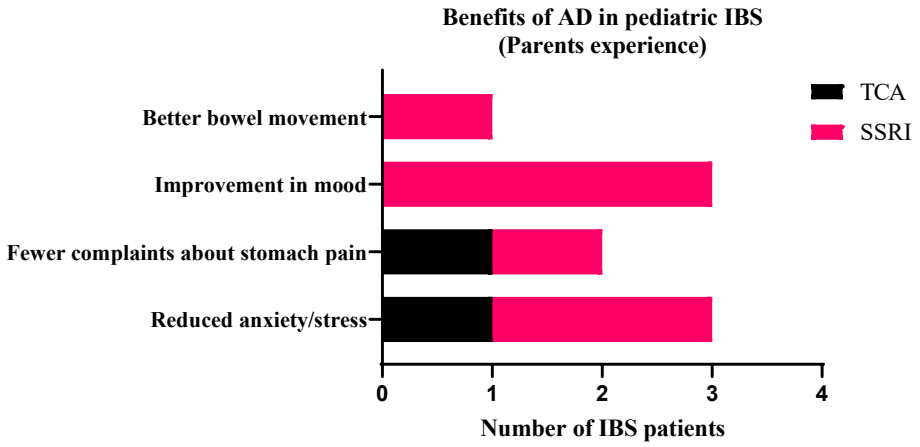


***Figure 6a: Observed benefits of antidepressants in IBS + pediatric group - Grouped bar chart representing benefits of SSRI and TCA in pediatric IBS management. Multiple responses were selected by each respondent (n=4). AD = antidepressant, TCA = Tricyclic antidepressants, SSRI = Selective Serotonin Reuptake Inhibitors.***

Survey from doctors showed that the most challenging reason for antidepressant prescription for pediatric IBS is non-adherence to a long-term treatment plan (81.8%) as well as rejection of antidepressant use for their child (72.7%) (Figure 6b).

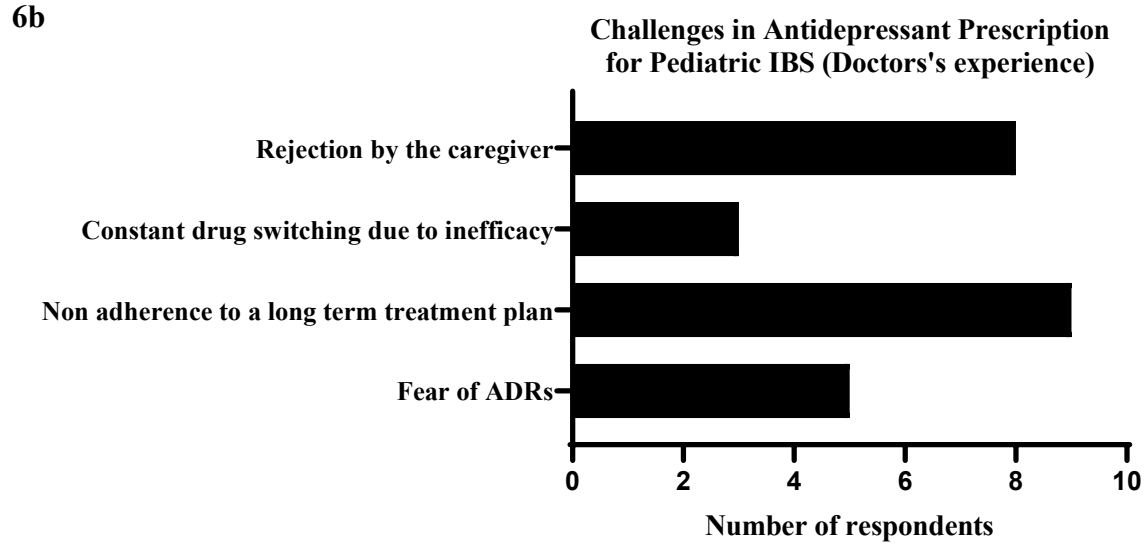


***Figure 6b: Challenges in antidepressant prescription (Doctor's perspective) - Bar chart showing various challenges faced by a medical professional while prescribing antidepressants in pediatric IBS care. Each respondent (n=11) was able to select multiple choices.***

### 3.6 Comparison of Commonly Observed Adverse Drug Reactions (ADRs) with Antidepressant Use for IBS management (Caregivers vs Doctors)

Among 4 caregivers who adhered to antidepressant treatment for their child's IBS management 50% reported that their child complained about frequent headaches and appetite changes with antidepressant use. Only 1 caregiver reported sleep issues with antidepressant use (Figure 7).

On the other end, medical professionals have reported mood swings (72.7%) as the most common adverse drug reaction (ADR) with antidepressants (AD) used by pediatric IBS patients. Restlessness (54.5%), GI side effects (45.4%), appetite changes (45.4%), and sleep issues (45.4%), were major side effects reported by medical providers. Headaches (9%) were the least reported ADRs of antidepressant as per their medical practice experience (Figure 7).

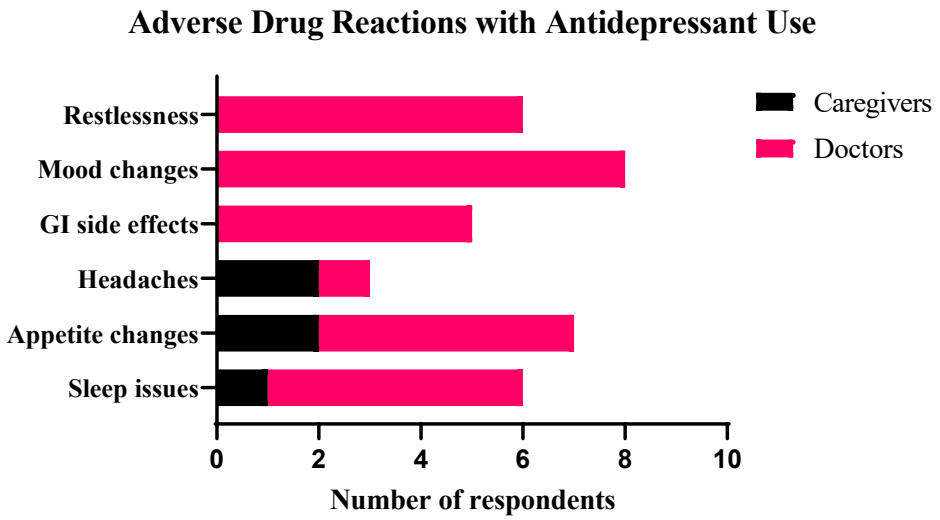


***Figure 7: Observed ADRs with antidepressant use - Grouped bar chart representing Adverse Drug Reactions (ADRs) with antidepressant use as observed by caregivers and doctors for pediatric IBS management. The responses from medical providers do not relate to the 10 IBS pediatric patients in this study. Multiple selections were allowed by each respondent for this question.***

### 3.7 Factors Affecting Re-evaluation of IBS Treatment Plan

Four factors were identified as the major reasons to re-evaluate the IBS treatment plan. They were changes/worsening IBS symptoms (75%) followed by no effect from current medication and type of treatment (use of antidepressants and cost) (50% each) and then side effects from current treatment (25%). The above reasons matched from a medical provider's perspective as well. Medical providers also reported that 10 % of caregivers are not comfortable with the type of treatment prescribed either due to the costs involved or because of the need for antidepressants for their child's IBS treatment plan (Figure 8).

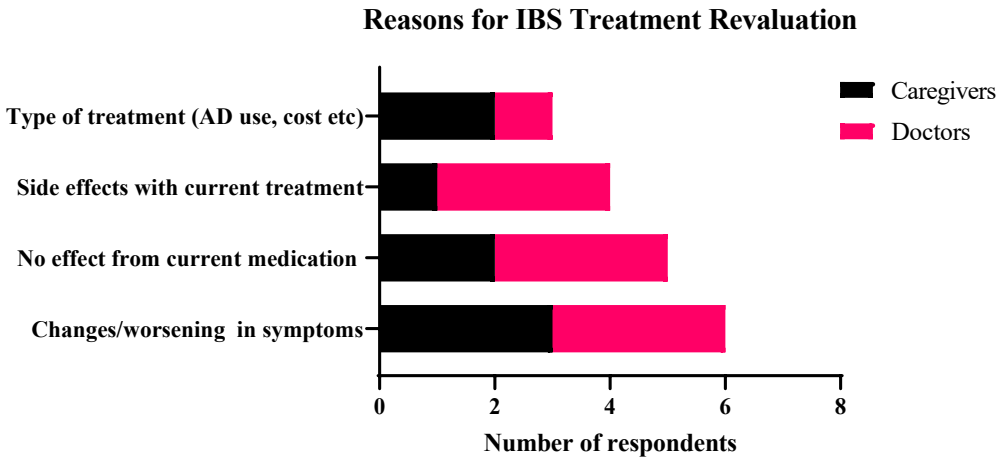


***Figure 8: Reasons for IBS treatment evaluation - Grouped bar chart representing difference in perspectives of caregivers and doctors to re-evaluate IBS treatment plan.***

### 3.8 Number of Visits to the Healthcare Professionals Office

The caregivers reported doctor visits anywhere from biweekly to quarterly which is inclusive of any additional complementary therapies. However, most medical specialists had pediatric IBS patients come every quarter (Figure 8).

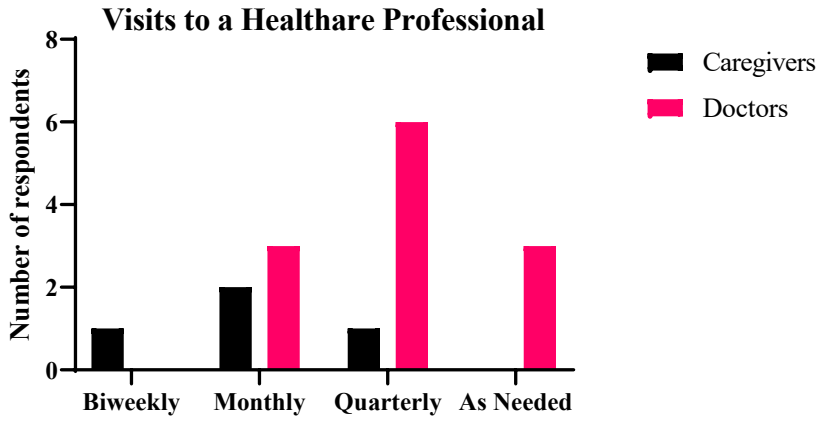


***Figure 9: Number of doctor visits (caregiver vs doctor recommendation) - Grouped bar chart representing the number of doctor visits by a caregiver (black) for their child's IBS treatment vs recommended frequency of follow-up appointments for pediatric IBS patients receiving antidepressant treatment (pink).***

### 3.9 Willingness To Utilize Genetic Testing For Antidepressant Use In Pediatric IBS Patients

Upon asking caregivers and medical providers whether or not they would be willing to utilize genetic testing for antidepressant choice and dosage for pediatric IBS, 20% of caregivers and 40% of medical providers said “yes”. Around 60% of caregivers and doctors would like to consider genetic testing for personalized IBS treatment in future. 20% of caregivers and 10% doctors denied the use of genetic testing for the prescription of antidepressants in children (Figure 10).

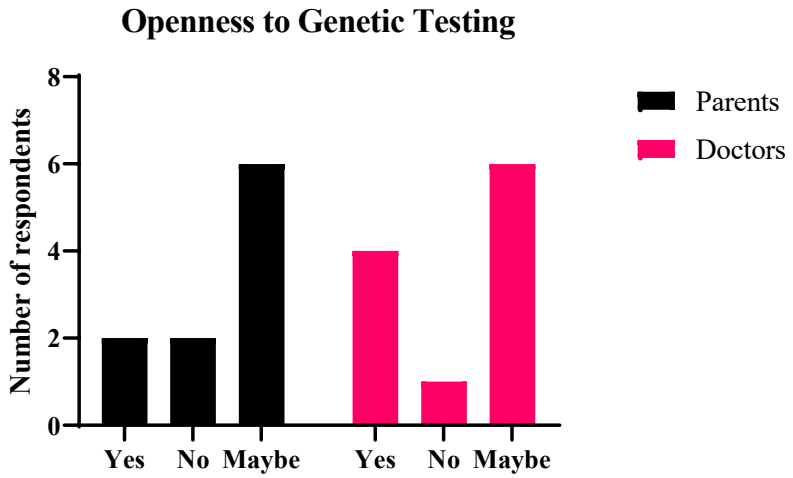


***Figure 10: Openness to genetic testing (caregivers vs doctors) - Bar chart showing willingness of caregivers (black) and doctors (pink) to utilize genetic testing for antidepressant choice and dosage for pediatric IBS patients.***

### 3.10 Awareness and Educational Resources

Fifty percent of caregivers and 63% of doctors are aware of ongoing research and utilization of genetic testing in pediatric IBS management (Figure 11a). Approximately 45% of doctors provide support resources to parents to further gain insights on pediatric IBS. However, sixty percent of caregivers of IBS pediatric patients reported that they do not have access to any support resources (Figure 11b).

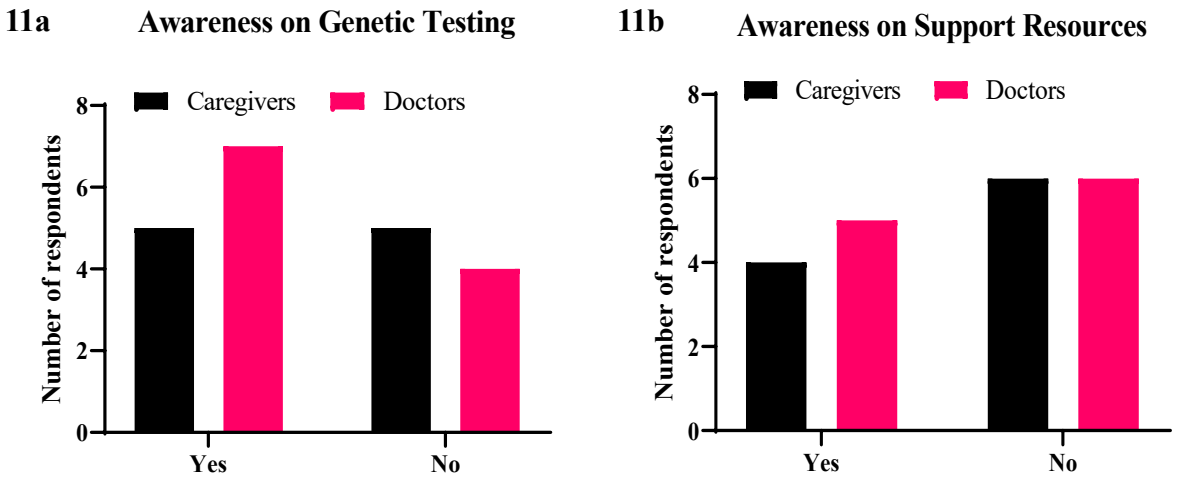


***Figure 11: Awareness on genetic testing and support resources (caregivers vs doctors) - Grouped bar chart showing (a) Awareness of caregivers (black) and doctors (pink) on the ongoing research in pediatric IBS. (b) Number of caregivers who have access to support resources (black) vs number of medical professionals providing support resources to caregivers of IBS patients (pink).***

# CHAPTER 4: DISCUSSION

IBS is a functional gastrointestinal disorder often accompanied by mental health problems that is difficult to diagnose and treat (Devanarayana & Rajindrajith, 2018; Paul et al., 2013; Rahman et al., 2017). The prevalence of IBS in children and adolescents under 18 years as reported by Korterink et al, in 2015 was about 8.8 % (Korterink et al., 2015). Since then, no global survey has been conducted that reports the prevalence of IBS specifically in children worldwide. Western lifestyle choices like unhealthy food habits, lack of physical activity, and cultural or professional competence are some of the major factors contributing to the increased prevalence of IBS globally (Sahoo & Padhy, 2017).

The prevalence of IBS in children varies across countries because of the differences in food habits, microbiome fingerprint, culture, early life events, socioeconomic status, awareness, and diagnosis criteria. Children from affluent families often suffer from family pressures, adapt to more western lifestyle and maybe more competitive among peers to maintain socioeconomic status which may contribute to increased prevalence of IBS in this subset of population (K.-Y. Huang et al., 2023; Karunanayake et al., 2022). Our survey that was conducted worldwide received the most responses from India and the United States. Based on the study by Rahman et al, 2017, the prevalence of IBS in children in India was between 4.2 -7.5%, and in the US is 2.8 – 5.1 % (Devanarayana & Rajindrajith, 2018; Rahman et al., 2017). However, in our study after 7 years, the percentage of confirmed pediatric IBS cases in India and the US have increased to 20% and 50% respectively. The difference in prevalence rates of pediatric IBS between developed and developing countries is contrasting from the review published by Devanarayana & Rajindrajith in 2018.

Each survey response for observed symptoms was assessed and matched to Rome IV criteria. The data showed that approximately 21.2% of children worldwide who reported 2 or more symptoms

along with recurrent abdominal pain had never been diagnosed with IBS. This subset of potentially IBS-positive patients belonged to developing countries like China, India, Pakistan, and the Philippines. In contrast, developed countries like Australia, Bangladesh, Sweden, United Arab Emirates (UAE), United Kingdom (UK), and the United States of America (USA) either showed complete IBS diagnosis or no IBS symptoms or the chances of potentially IBS positive was less than 1%. These differences reflect the current awareness among caregivers and diagnostic approaches worldwide.

Despite multiple tools available online and the recognition of IBS awareness month in April every year with the celebration of World IBS Day on April 19th (IFFGDAdmin, 2024), it is surprising to observe gaps in the perspectives of healthcare providers and caregivers. The survey data from caregivers suggested that 50% of parents are not aware of any ongoing research and development in pediatric IBS, and about the same proportion of respondents were not given support resources from their child's medical provider as well. IBS diagnosis relies mainly on the history of symptoms that include frequency of abdominal pain, occurrence of anxiety/depression, and presence of any early life events. Due to the lack of awareness, parents/caregivers often fail to provide a definite response on the type, intensity and frequency of symptoms that could be used to diagnose IBS based on Rome IV criteria. Additionally, a parent might not value disclosing any personal events in the family to the medical provider thus adding to the incomplete medical history of their child (Koppen et al., 2017; Paul et al., 2013).

Upon onset of symptoms, the biggest challenge for a clinician is missed diagnosis. The survey data suggests that the approach to diagnosing pediatric IBS differs among general practitioners and gastroenterologists. Based on the survey data, general practitioners would go for blood and stool tests followed by an endoscopy or colonoscopy whereas gastroenterologists follow Rome criteria

while diagnosing IBS in children. There is also heterogeneity in the version of Rome criteria for pediatric IBS diagnosis worldwide (Paul et al., 2013). Parents/caregivers do not directly go to a specialist unless referred by their primary care provider or pediatrician. By prescribing multiple diagnostic tests, a general practitioner would approach diagnosis holistically to rule out the presence of any organic disease. Moreover, there is a lack of any available laboratory tests to specifically point toward IBS.

To rule out any possibility of infection or underlying condition, medical providers often recommend multiple diagnostic tests including blood, stool, and imaging by endo/colonoscopy (Cristofori et al., 2014). Additional tests like ultrasound, x-ray, lactose breath hydrogen tests, urine analysis, etc. may be performed to rule out any organic abnormality like celiac disease or colitis (*Articles*, n.d., *Diagnosis of Irritable Bowel Syndrome in Children*, 2021). Based on our survey data 50% of children underwent 2 or more diagnostic tests and 30% of them received 3 or more treatments including dietary and psychiatric interventions. The average healthcare costs of IBS-D-insured patients alone can go up to $13,000 annually including office visits, prescription refills, and outpatient services as reported in 2017 (Buono et al., 2017). Treatment of IBS usually requires a multifaceted approach involving general practitioners, pediatricians, gastroenterologists, and psychiatrists. Certain long-term alternative treatments like hypnotherapy, cognitive behavioral therapy (CBT) by a psychiatrist, and/or a suitable diet plan by a dietician add to the initial costs as mentioned before. The lack of awareness among caregivers, the time taken to diagnose IBS by a general practitioner to a specialist, the unavailability of specific diagnostic tools for IBS, and the costs involved often delay treatment and can be burdensome to the caregiver both mentally and financially.

Due to the involvement of the gut-brain axis, many IBS patients exhibit psychological co-morbidities like anxiety and depression. Psychological triggers like stress and early life events can impact intestinal motility, secretion, and permeability. Under chronic stress conditions, the crosstalk between the HPA axis and microbiota-gut-brain axis can alter the neuro-endocrine-immune pathways often resulting in symptom flare-ups (Devanarayana & Rajindrajith, 2018; Qin et al., 2014). Therefore, neuromodulators like antidepressants are utilized as a second line of treatment in children and adolescents suffering from IBS (Devanarayana & Rajindrajith, 2018; Kaminski et al., 2012; Qin et al., 2014).

The survey data from medical providers showed that tricyclic antidepressants (TCAs) were the preferred choice (45%) for pediatric IBS management. However, SSRIs (Prozac and Zoloft) were the choice of antidepressant that were utilized by pediatric IBS patients. The use of TCAs in the pediatric population is not approved by the FDA due to safety concerns. Only imipramine is approved by the FDA for enuresis in children. For Major Depressive Disorders (MDD), FDA has approved SSRIs like Escitalopram and Fluoxetine for pediatric patients (Dwyer & Bloch, 2019). The anomaly in preference of antidepressants for pediatric use for management of IBS could be explained by the efficacy and safety profile of the two classes of antidepressants. Due to off-label use of TCA based on the clinical trial data in the adult population, it is a huge challenge to comfort caregivers to accept tricyclic antidepressant treatment for their child's IBS management (Ballinger, 2023).

The use of antidepressants in IBS pain management has shown clear benefits in adult patients. However, this is not the same in children. In our survey with caregivers about the benefits observed in their child with SSRI antidepressants, most of the caregivers reported only improvements in mood and anxiety along with slight benefits in bowel movement. Only 1 patient reported

improvement in abdominal pain with SSRI use. A clinical study (double-blind randomized placebo-controlled trial) conducted by Saps *et al,* 2009, United States with 90 children (8-17 years) was conducted for 4 weeks to evaluate the overall benefit of amitriptyline (10mg/day) in children (weight < 35 kg) suffering from FAPD. The study reported 58% overall treatment success with the amitriptyline group, but no significant improvement was seen in pain frequency and intensity. Three children withdrew from the trial due to adverse events (fatigue, headaches, and dizziness). In another study (double-blind randomized placebo-controlled trial) by Bahar *et al.,*2008, United States, did an 8-week study with amitriptyline with 33 children (12-18 years) suffering from FAPD. About 39% of the amitriptyline group showed an overall improvement in quality of life but no improvement in pain intensity and frequency was seen. Similarly, another study (double-blind randomized placebo-controlled trial) by Roohafza *et al.,* 2014, Iran, with 115 children (6-18 years) also did not show any therapeutic improvement in IBS symptoms with 4-week treatment with citalopram (10mg/day, first week and 20 mg/day for 3 weeks) (Devanarayana & Rajindrajith, 2018; Rexwinkel et al., 2021). To date, due to the small sample size, heterogeneous study design, and fewer enrollment of children in the clinical study due to associated adverse drug reactions, there is limited knowledge on the choice and dosage of antidepressants for pediatric use (Alyasi et al., 2023; Bonilla & Nurko, 2018; Oh et al., 2020; Rexwinkel et al., 2022).

Generally, treatments with antidepressants take some time (>4 weeks) to see some effects in improving abdominal pain in IBS patients (Bonilla & Nurko, 2018). The survey data from medical providers suggests that the major challenge while prescribing antidepressants to pediatric patients is non-adherence to a long-term treatment plan. Even though there is some data from clinical trials on the use of antidepressants conducted with adult IBS patients, the dosage cannot be matched in pediatric patients. With limited knowledge of the choice and dosage of these antidepressants,

healthcare professionals usually have different dosing strategies for different classes of antidepressants for pediatric patients. SSRIs are started at a low initial dose and titrated up to 20 mg/day. However, TCAs are underdosed at 0.2-0.5 mg/kg/day (Chiou & Nurko, 2014) compared to 1-5 mg/kg/day due to fear of adverse drug reactions such as gastrointestinal irritation, irritability, and in extreme cases suicidal ideation and serotonin syndrome (Hazell & Mirzaie, 2013). No data suggests that conservative dosing will have any benefits in treating the symptoms. Nonetheless, clinicians continue to prescribe low-dose antidepressants that may not be able to achieve its therapeutic index and may fail to provide any efficacy. Hence, caregivers often give up on the treatment plan enabling the doctor to constantly switch drugs (Bonilla & Nurko, 2018; Dwyer & Bloch, 2019; Seetharaman et al., 2022; Taylor et al., 2010).

General antidepressant adverse drug reactions in pediatric patients as reported from the survey data are gastrointestinal irritability, mood swings, and restlessness. In severe cases, suicidal ideation and serotonin syndrome have also been reported (Dwyer & Bloch, 2019; Tan et al., 2013). Amitriptyline is metabolized by CYP2C19 into its secondary amines which are further transformed into inactive compounds by CYP2D6. On the other side, SSRIs like Citalopram & Escitalopram are mainly metabolized by CYP2C19 with minor involvement of CYP2D6 and CYP3A4 in their metabolism. The Clinical Pharmacogenetics Implementation Consortium (CPIC®) recommends dose reduction or alternative therapy if an individual is a poor metabolizer (PM) of CYP2C19 (Aka et al., 2017; Dean, 2017). CYP2D6 is a highly polymorphic gene with over 100 allelic variants but only a few are clinically relevant that lead to a PM phenotype - CYP 2D6*3A, CYP 2D6*4B, and CYP 2D6*5. Similarly, variants of CYP2C19 like CYP2C19*2 lead to a PM phenotype, and CYP2C19*17 results in an ultra-metabolizer (UM) phenotype (Austin-Zimmerman et al., 2021; Bondy, 2005; Dean, 2017; X. Huang et al., 2021; Petrović et al., 2020).

CYP2C19 and CYP2D6 polymorphisms can vary among different ethnic groups and a PM phenotype is at a higher risk of toxicity with the use of these specific antidepressants (Bondy, 2005; Dean, 2017). Because CYPs are an important contributor in impacting drug efficacy and safety, the research hypothesized to consider pharmacogenomic testing in pediatric patients to aid healthcare professionals in choosing the adequate class of antidepressants and optimum dosage for a targeted effect. Hence, we asked both caregivers and healthcare professionals if they would opt for genetic testing in the future. We observed that >50% of both groups would like to utilize genetic testing for personalized medicine in the future. As of December 31st, 2023, 111 cases of amitriptyline adverse drug reactions in children of age groups 3-11 years and 237 cases of age group 12-17 years have been reported on the FDA Adverse Events Reporting System (FAERS) Public Dashboard. Five cases of 237 have reported serious adverse reactions like completed suicide and cardiorespiratory arrest with the use of amitriptyline in children aged 12-17 years. (Qlik Sense, n.d.). These adverse events are most likely due to high plasma concentrations of amitriptyline and nortriptyline which in turn are a result of loss of function of either CYP2D6 or CYP2C19 or both (Buhagiar et al., 2022; Dean, 2017). Hence, genotyping of CYP450 enzymes and other relevant, actionable biomarkersfor antidepressant choice can be beneficial in catering to personalized medicine and achieving quicker relief without any risk of side effects.

While genetic tests like are available in the market with proven evidence of improved depressive symptoms and lower hospitalization rates due to adverse effects, their current use is limited ("Pharmacogenomic Testing for Psychotropic Medication Selection: A Systematic Review of the Assurex GeneSight Psychotropic Test.," 2017). It is surprising to note that only two healthcare professionals in our survey used genetic testing to determine the choice and dosage of antidepressants for pediatric IBS. Besides the cost of the test (average $330), it is difficult to

understand the possible reasons why genetic testing is not frequently utilized (Genetic Testing Cost | Genetic Testing Insurance | GeneSight, n.d.).

### 1.1 Limitations

The current study has attempted to bridge the gap between the perspectives of caregivers and healthcare professionals in approaching pediatric IBS treatment. However, a low sample size compromises the ability to precisely assess the current awareness and diagnostic trends of pediatric IBS. Moreover, the data is collected only for a period of 2 months, which limits the ability to collect responses worldwide. The study design is through an online platform which limits the responses to only individuals with internet access. During the research, the major challenge was to convince both healthcare professionals and caregivers to agree to take the survey. At the time of the survey period, the author found a parent community on Facebook™ with approximately 1600 parents whose children had complete diagnoses of IBS but only less than 1% agreed to take the survey. The reluctance rate in filling out the survey might have reduced the actual response rate thus impacting the true sample size. In the future, perhaps granting money to fund incentives like gift cards to survey takers and distributing the survey through an expert in the field in various countries might be helpful in getting more respondents and achieving statistically significant results (How to Increase Online Survey Response Rates, 2023).

# CHAPTER 5: FUTURE DIRECTIONS AND CONCLUSIONS

As previously stated, stress-induced IBS is an escalating epidemiological issue, particularly in children and adolescents. It is crucial to recognize that anxiety and depression during IBS episodes can result not only in physical discomfort but also impact emotional development in the long term. Additionally, untreated IBS can lead to a weakened immune system and make the patient more susceptible to infections.

Conventional psychotherapy treatments like hypnotherapy, CBT, and mindfulness are available but can be expensive and require expert personnel to perform disease-specific interventions. Given the challenges and complexity of the disease in children and adolescents, caregivers need to comprehend the necessity of adhering to an antidepressant treatment for their child as these medications will help with the management of IBS symptoms and improve their quality of life. Additionally, medical practitioners should strive to provide a safe and effective treatment regimen, taking genetic variation for drug metabolism and response into account.

A potential solution in delivering personalized treatment can be achieved through PGx testing. By analyzing an individual's genetic profile, PGx testing can help identify specific DME gene polymorphisms and help predict a patient's response to treatment. The application of PGx in tailoring appropriate antidepressant selection and dosage allows healthcare providers to select the most appropriate antidepressant and dosage for a given patient, maximizing the chances of success, and minimizing adverse effects. In the context of pediatric IBS, PGx testing can play a crucial role in optimizing treatment regimens, promoting better outcomes, and addressing the unique challenges posed by this condition, ultimately improving the quality of life for affected children and adolescents.

The current study attempted to determine the current awareness and treatments for pediatric IBS, and challenges associated with treatment plans and assessed the confidence of healthcare professionals in choosing suitable antidepressants for pediatric IBS treatment through a survey-based questionnaire. It was observed that the prevalence of pediatric IBS is more in developed countries suggesting less awareness of pediatric IBS among caregivers in developing countries. Moreover, parents get emotionally stressed when their child is in pain and often engage in multiple hospital visits to find an effective treatment. This non-adherence to a long-term treatment plan often requires revaluation of the treatment that may involve constant drug switching. Lack of awareness, non-availability of specific tests, and limited knowledge on the use of antidepressants for pediatric IBS due to sparse clinical trials in children are some current gaps that set the stage for further investigation into this often-overlooked aspect of IBS.

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## APPENDIX 1

### Approval Letter from Harrisburg University-Institutional Review Board

Date: December 27, 2023

IRB File No. EXP452781

The review of your protocol titled “Application Of Pharmacogenomics in Choosing Antidepressants for Children Suffering from Stress-Induced Irritable Bowel Syndrome” is now complete. The project has been approved as an expedited study for a one-year time period expiring on Dec 18, 2024.

Please note that HU-IRB approval policies require that you adhere strictly to the protocol as last reviewed by the IRB and that any modifications must be approved by the IRB before they can be implemented. Adverse or unexpected events must be reported to the IRB as soon as possible with an indication from the Principal Investigator as to how, in the view of the Principal Investigator, these events affect the continuation of the protocol.

Finally, it is the responsibility of the Principal Investigator to ensure that any required ethical guidelines and approvals of any outside facilities or institutions are obtained and filed with the IRB prior to the initiation of any research.

Please quote your IRB file number EXP452781 on future correspondence.
Congratulations and best of luck in conducting your research.

Best,

Dr. Kayden Jordan, IRB Chair

1. **Survey for doctors.**

**Subject: Invitation to Contribute to Advancing Pediatric IBS Care through Pharmacogenomics**

Dear Medical Professionals,

I hope this message finds you well. My name is Tripta Rughwani, and I am a graduate student of Harrisburg University of Science and Technology working on a significant research study for my thesis in the field of personalized medicine and pediatric Irritable Bowel Syndrome (IBS). Stress is one of the major factors known to trigger IBS symptoms. In particular, children and adolescents are the most affected group suffering from IBS worldwide. While antidepressants have shown some efficacy, prescribing a universal drug is challenging due to the variability in IBS symptoms and the levels of depression/anxiety among patients. Moreover, it is difficult to convince caregivers to try antidepressant treatment for their child due to concerns about associated side effects. Pharmacogenomics is an emerging field that could resolve the problem of "one drug fits all". Our study focuses on the application of pharmacogenomics in selecting antidepressants for children diagnosed with IBS. We aim to understand the challenges and opportunities in optimizing treatment regimens for young IBS patients as well as your thoughts on implementing genetic testing in the choice and dosage of antidepressants. Your experience and knowledge are of utmost importance in shaping the future of pediatric IBS care.

**Title of Research Study: Application Of Pharmacogenomics in Choosing Antidepressants for Children Suffering from Stress-Induced IBS.**

**Why Your Participation Matters:**

**Medical Expertise:** Your clinical expertise in pediatric gastroenterology is invaluable in shedding light on the medical aspects of our study.

**Improving Patient Outcomes:** Your input can lead to more effective and personalized treatment options for young IBS patients, ultimately improving their quality of life.

**Advancing Medical Knowledge:** Your participation contributes to the advancement of medical knowledge in the field of IBS and personalized medicine.

**Participation Details:**

Your involvement in our study is as straightforward as completing a brief questionnaire. Your responses will remain confidential and anonymous. The survey is completely optional, and you may quit at any time. The nature of the subject matter is contained within the Qualtrics software. You are under no obligation to complete the survey and may choose to opt-out at any time. This survey is completely anonymous and NO private information including name, DOB, address, phone number, bank account number, SSN, TIN, IP address, or GO location will be collected from the respondents. The only information that will be recorded is the respondent's answers to the questions contained within the survey. This survey has been reviewed and approved by the Harrisburg University Institutional Review Board and complies with all ethical research requirements. The survey will take approximately 10 minutes of your valuable time. You can come back anytime to complete the responses.

If you are willing to participate, please consent below to proceed with the survey [Survey Link].

If you have any questions or need further information about our study, please do not hesitate to reach out to me via email at trughwani@my.harrisburgu.edu or by phone at +1 (469) 929 4673 [also available on WhatsApp for survey takers outside US].

Your participation is a pivotal part of this research, and your insights can bring us closer to providing better care for children with IBS.

Thank you for considering this request, and we look forward to your valuable contribution to our study.

Warm regards,

Tripta Rughwani

Harrisburg University of Science and Technology

**I have reviewed the research summary and consent to participate in the questionnaire.**

**Y/N**

**Section 1: General Information**

1. Medical Specialty: pediatrician/ gastroenterologist/ general practitioner/ nurse practitioner/ psychiatrist/ other (please specify)

**Section 2: Pediatric IBS Diagnosis and Assessment**

1. What diagnostic criteria or tests do you commonly use to diagnose IBS in pediatric patients?
    - Rome IV Criteria
    - Blood Tests
    - Stool Tests
    - Endoscopy or Colonoscopy
    - Other (please specify)
2. In your experience, what are the most common symptoms of pediatric IBS that you encounter (select all that apply)?
    - Abdominal pain

- Diarrhea
- Constipation
- Bloating
- Other (please specify)

3. Have noticed any depression or anxiety disorders in pediatric patients with IBS? Y/N

4. What is the most common age group presenting with IBS symptoms?

- 4 to 7 years
- 8 to 12 years
- 13 to 17 years

5. On a scale of 0 to 5, how severe are anxiety/depression symptoms with pediatric patients with IBS?

5 – very severe, 4- severe, 3- manageable, 2-moderate, 1- mild, 0 - nonexistent

**Section 3: Treatment Approaches for Pediatric IBS**

1. What are the standard treatment options you recommend or prescribe for pediatric patients with IBS? (Select all that apply)

- Dietary and lifestyle changes
- Antidepressant medication
- Other medications (please specify)
- Complementary therapies (e.g., probiotics, cognitive-behavioral therapy)

2. Have you ever prescribed antidepressant medications for pediatric patients with IBS? Y/N

3. If yes, what factors influence your decision to use antidepressants in the treatment of pediatric IBS? (Select all that apply)

- Severity of symptoms
- Lack of response to other treatments
- Co-occurring anxiety or depression
- Other (please specify)

4. What is the most common antidepressant prescribed to pediatric patients with IBS?

Drop down list including : fluoxetine (Prozac, Flunil), sertraline (Zoloft, Abisert), Duloxetine (Cymbalta, Drizalma Sprinkle), Escitalopram (Lexapro, Cipralex) , Fluvoxamine (Luvox), Citalopram (Celexa, Akarin, C Pram S), Tricyclic antidepressants (amitriptyline, imipramine etc) other

**Section 4: Medication Selection and Dosage**

1. How do you typically determine the choice of antidepressant and dosage for a pediatric patient with IBS?

- Patient's symptoms and history
- Guidelines and clinical experience
- Pharmacogenomic (PGx) testing
- Other (please specify)

2. What are some challenges that you face while prescribing antidepressants to children? (Select all that apply)

- Fear of adverse drug events
- Constant drug switching due to inefficacy.

- Rejection by the caregiver on the use of antidepressant for their child
- Nonadherence to a long term treatment plan

3. Do you consider pharmacogenomic or genetic (PGx) testing when prescribing antidepressants for pediatric IBS patients? Yes/No/Not right now, but would like to consider in future

**Section QA:**

1. For Quality Assurance purpose, please select the number "2" from the options below.

- 4
- 6
- 2
- 1

**Section 5: Monitoring and Follow-up**

1. What is the recommended frequency of follow-up appointments for pediatric IBS patients receiving antidepressant treatment in your practice?

- Biweekly
- Monthly
- Quarterly
- Semi-annually
- Annually
- As needed

2. What signs or symptoms prompt a reevaluation of the treatment plan for pediatric IBS patients on antidepressants? (Select all that apply)

- Worsening symptoms
- New side effects
- Lack of improvement
- Parents are not comfortable with type of treatment
- Other (please specify)

**Section 6: Challenges and Adverse Effects**

1. In your experience, what are the most common challenges or adverse effects associated with the use of antidepressants in pediatric IBS treatment? (Select all that apply)

- Gastrointestinal side effects
- Mood changes
- Sleep disturbances
- Appetite changes
- Restlessness/ irritability
- headaches
- Seizures
- Heart problems
- Suicidal ideation
- Other (please specify)

**Section 7: Information and Support Resources**

1. Do you provide caregivers and pediatric IBS patients with information on support resources or educational materials? If so, please describe these resources. Y/N

**Section 8: Research and Future Developments**

1. Are you aware of ongoing research or developments in the field of pediatric IBS, particularly related to personalized medicine and the use of genetic testing? Y/N
2. Would you be willing to prescribe genetic testing for antidepressant choice and dosage in future? Y/N

2. **Survey for parents/caregivers.**

**Title of Research Study: Application Of Pharmacogenomics in Choosing Antidepressants for Children Suffering from Stress-Induced IBS.**

**Investigator:** Tripta Rughwani

**Key Information:** This survey is part of a graduate research project. The survey is completely optional, and the respondent can quit at any time. The nature of the subject matter is contained, and the questions might be distressing to some respondents. The respondent is under no obligation to complete the survey and may choose to opt-out at any time. This survey is completely anonymous and NO private information including name, DOB, address, phone number, bank account number, SSN, TIN, IP address, or GO location will be collected from the respondents. The only information that will be recorded is the respondent's answers to the questions contained within the survey. This survey has been reviewed and approved by the Harrisburg University Institutional Review Board and complies with all ethical research requirements. The following is a summary of this study to help you decide whether to be a part of the survey.

Note: You do not need any scientific background for the survey. We value your honest opinion based on your experience. The survey does not have to be completed in one setting. You can go back to finish the survey anytime.

**Why am I being invited to take part in a research study?**

We are inviting parents/caregivers of children (4-17 years) to complete this survey on "Personalized medicine and IBS treatment" to revolutionize the current treatment regimen for IBS patients, particularly the choice of antidepressants.

**How will my participation help?**

We understand that caring for a child with IBS can be challenging. Our experiences as a caregiver are invaluable and can pave the way for better care options for children with IBS. That's why we are reaching out to all the superheroes today. Your thoughts will help create better, personalized treatments for kids with IBS. By sharing your experiences, you're assisting caregivers, like yourself, in making smart choices for treatments based on a child's unique traits. We value your honest opinion.

**What do I need to do if I volunteer to participate in the survey?**

If you choose to participate in the survey, you will be asked to do the following things based on a protocol reviewed by the Harrisburg University Institutional Review Board:

1. You will be provided with a description summarizing an overview of the research (above).
2. You will be asked to review and sign/agree a consent form (provided below).
3. You will be asked preliminary questions to ensure your eligibility for the study upon consent.

4. If eligible, you will be asked to answer a short questionnaire that will take no more than 15 mins.

**Is there any way being in this study could be bad for me?**

We do not anticipate any risks involved. The survey consists of short questions that are contained within the Qualtrics software. We will not collect any personal identifiable information from the respondents and all responses will be kept confidential. Some questions might be distressing, and the respondent can choose to skip or opt out of the survey at any time. The participation is completely voluntary.

**Who can I talk to if I have questions?**

If you have questions, concerns or complaints, please reach out to Tripta Rughwani via email at trughwani@my.harrisburgu.edu or by phone at +1 (469) 929 4673 (also available on WhatsApp for responders outside US).

This survey has been reviewed and approved by the Harrisburg University Institutional Review Board and complies with all ethical research requirements. You may contact them at IRB@harrisburgu.edu if you are unable to reach the investigator and/or you have questions about your rights as a subject.

By proceeding ahead, you have agreed to consent that you have been provided with information of the scope of the study, have been informed about the risks associated and want to voluntarily participate in this research study. Do you still wish to proceed with the survey?

- YES
- NO

**Section 1: Preliminary Screening**

1. Are you a parent/caregiver of a child who is aged between 4-17 years? Y/N

2. Does your child frequently complain about stomach pain? Never/Sometimes/Always

3. Does your child show signs of anxiety and often misses school due to any stress? Never/Sometimes/Always

4. Do you think your child complains about frequently being bloated, has severe constipation or diarrhea? Yes/No/Maybe

**Section 2: General Information**

1. Gender of the child: Male/Female/Other (please specify)
2. Age of child:
3. Country of Residence: [drop down list from Qualtrics]

**Section 3: IBS Diagnosis (Reminder: All responses are anonymous and your answers will be kept confidential)**

1. Does your child have any of the following symptoms? Select all that apply:
    - Stomach pain
    - Changing bowel habits (constipation/ diarrhea)
    - Bloating
    - Gas
    - Anxiety
    - Depression
    - Repeated gastrointestinal infections
    - Any other mental health conditions (please specify) -
2. Has your child been diagnosed with IBS by a healthcare professional? Yes/No

3. What diagnostic tests or criteria were used for the IBS diagnosis? (Select all that apply)

- Rome IV Criteria
- Blood Tests
- Stool Tests
- Endoscopy or Colonoscopy
- Other (please specify)

**Section 4: Treatment for Pediatric IBS (Reminder: All responses are anonymous and your answers will be kept confidential)**

1. What treatments, if any, have been recommended or prescribed for your child's IBS? (Select all that apply)

- Dietary and lifestyle changes
- Antidepressant medication
- Stress management therapy/ hypnotherapy
- Other medications (please specify)
- Complementary therapies (e.g., probiotics, cognitive-behavioral therapy)

**Section 5: Antidepressant Use (Reminder: All responses are anonymous and your answers will be kept confidential)**

1. Has your child been prescribed an antidepressant as part of their IBS treatment? Y/N

2. If yes, please specify the name of the antidepressant medication(s): [ I can also provide a list of approved antidepressants for pediatric use – fluoxetine (Prozac, Flunil), sertraline (Zoloft, Abisert), Duloxetine (Cymbalta, Drizalma Sprinkle), Escitalopram

(Lexapro, Cipralex) , Fluvoxamine (Luvox), Citalopram (Celexa, Akarin, C Pram S), Tricyclic antidepressants (amitriptyline, imipramine etc) other ] – maybe a dropdown list

3. Did you adhere to the antidepressant treatment if prescribed? Never/Sometimes/Always

4. Did you deny antidepressant treatment if prescribed? Y/N

5. What were the reasons to deny the antidepressant prescription in case you chose to deny antidepressants? Select all that apply:

- Inefficacy of antidepressant
- Did not believe that my child has depression/ anxiety
- Fear of adverse reactions
- Long term use so its expensive
- Fear of constant drug switching

6. How was the choice of antidepressant and dosage determined for your child's IBS treatment?

- By healthcare provider
- Genetic testing

**Section QA:**

1. For Quality Assurance purpose, please select the number "2" from the options below.

- 4
- 6
- 2

- 1

**Section 5: Opinion on Genetic Testing for Medication Selection and Dosage**

1. Are you familiar with genetic testing, which helps personalize medication selection and dosing based on genetic factors? Y/N

2. Have you or your child undergone genetic testing as part of the IBS treatment decision-making process? Y/N

3. Would you be interested in your child undergoing genetic testing to assist in antidepressant medication selection for IBS treatment? Y/N/Maybe

**Section 6: Antidepressant Treatment Experience <u>(Reminder: All responses are anonymous and your answers will be kept confidential)</u>**

1. Please select all benefits or positive outcomes you've observed in your child due to the antidepressant treatment for IBS.

- Improvement in mood
- Reduced anxiety/ stress
- Fewer complaints about stomach pain
- Less gastrointestinal infections
- Other -------
- None
- I did not have any antidepressant treatment for my child.

2. Have there been any adverse effects or challenges related to the use of antidepressants in the IBS treatment for your child? Y/N

3. Select all adverse events related to antidepressant use for IBS treatment for your child.

- Sleep issues
- Restlessness/ irritability
- Headaches
- Appetite changes
- Stomach upset/ Nausea
- Fatigue
- Seizures
- Heart problems
- Suicidal ideation
- Others (please specify)

**Section 8: Follow-up and Monitoring**

1. How often does your child have follow-up appointments or check-ins with their healthcare provider regarding IBS treatment? (include all appointments for doctor visits + alternative treatment visits)

- Biweekly
- Monthly
- Quarterly
- Biannually
- Annually
- As needed

2. What is the primary sign or symptom that prompt a reevaluation of the treatment plan for your child's IBS?

- Any side effects

- No effects
- Changes in symptoms
- Type of treatment
- Costs and medical insurance coverage

**Section 9: Support and Information**

1. Are you aware of support resources or educational materials available to caregivers and patients with pediatric IBS? Y/N