Review Article

Improving the Treatment Response of Patients with Irritable Bowel Syndrome: Implementing a Second-Generation Artificial Intelligence System for Overcoming Resistance

Anat Hershko-Moshe, Yaako’v Hasin, Anat Nevo-Shor, Ohad Etzion, and Yaron Ilan

1Faculty of Medicine, Department of Medicine, Hebrew University, Hadassah Medical Center, Jerusalem, Israel
2Department of Gastroenterology and Liver Diseases, Soroka Medical Center, Israel
3Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel

Correspondence should be addressed to Yaron Ilan; ilan@hadassah.org.il

Received 16 June 2022; Accepted 12 September 2022; Published 26 September 2022

Copyright © 2022 Anat Hershko-Moshe et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Irritable bowel syndrome (IBS) is a common functional disorder. The syndrome’s multifactorial pathophysiology makes it challenging to design effective therapies. The present paper reviews several therapeutic approaches to treating IBS, highlighting the challenges of losing response over time to therapies. Here, we present the relevance of chronobiology in biological systems focusing on the potential of chronotherapy for IBS. Artificial intelligence- (AI-) based approaches have been developed over the last few years to improve the diagnosis, therapeutic approaches, and monitoring of patients with various diseases. We discuss the use of first-generation AI platforms and their limitations in clinical practice and present the establishment of a second-generation system designed to overcome obstacles in managing these patients. The system identifies costly patients and those who do not respond to therapies and may benefit from algorithm-based therapies. We present a patient-tailored approach for improving the response to therapy in IBS using an AI-based algorithm. This system provides a tool for a patient-tailored monitoring system. The second-generation AI system can provide a comprehensive tool for improving the diagnosis and therapy and monitoring of patients with IBS.

1. Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder. IBS is diagnosed according to patterns of gastrointestinal symptoms as described by the Rome diagnostic criteria [1]. IBS is characterized by abdominal pain and altered bowel habits without specific organic pathologies. Patients with IBS are classified into four subtypes: IBS with predominant constipation (IBS-C), predominant diarrhea (IBS-D), mixed bowel habits (IBS-M), and the unclassified subtype (IBS-U) [2]. IBS affects between 5% and 10% of healthy individuals at any point in their lives [3]. In most patients, it has a relapsing and remitting course. IBS has considerable effects on quality of life. A combination of environmental, infectious, genetic, microbiome, immune, diet, and gut-brain interaction-associated parameters underlies the pathogenesis of IBS [1]. These factors result in motility disturbances, visceral hypersensitivity, and altered central nervous system (CNS) processing. Both nonpharmacological and pharmacological therapies can help control IBS symptoms but do not provide relief to a significant proportion of patients [4–11].

In the present paper, we review some therapeutic approaches to treating IBS, highlighting the loss of response over time to therapies. We discuss the relevance of chronobiology in patients with IBS. The use of artificial intelligence-
(AI-) based approach was described. We focus on establishing a second-generation algorithm to overcome some of the main obstacles in treating IBS.

2. Treatment for IBS: Lack of Curable Therapies, Drug Resistance, and Low Response Rates

IBS therapy is aimed at providing symptomatic relief for diarrhea, constipation, and pain. While some patients respond well to nonpharmacological treatment, many require pharmacological treatment. Symptom-oriented pharmacological treatment algorithms manage many patients with IBS who fail to improve their lifestyle or follow psychological interventions [12]. Notably, single-agent therapy rarely relieves the symptoms in all patients [4, 13–17].

2.1. Pharmacological Treatments. Antidepressants and central neuromodulators can treat IBS. IBS is a disease caused by multifactorial elements linked with psychological disorders. Patients with IBS suffer from higher rates of anxiety and depression [18]. Psychological components may alter pain thresholds and cause visceral hyperalgesia [19]. Disturbance in the brain-gut axis is associated with IBS symptoms. The autonomic nervous system connects the CNS to the enteric nervous system (ENS). Disruption of this pathway may lead to constipation and diarrhea [20]. Antidepressants are a second-line treatment for IBS. Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) affect the CNS and gastrointestinal motility through serotonergic receptor activation and lead to symptom relief [21]. Relief in somatic but not in psychiatric symptoms was described with a lower dosage of TCA [20, 22]. TCA was more favorable for symptom relief in IBS-D and SSRI in IBC-C [23]. The long-term beneficial effects of antidepressant therapies on IBS are yet to be determined.

Vitamin D deficiency is associated with IBS symptoms, and its supplementation may be beneficial. However, the use of vitamin D in patients with IBS remains controversial. A case-control study showed a significantly higher prevalence of vitamin D deficiency in patients with IBS than in healthy individuals (82% vs. 31%). A randomized double-blind study reported significant improvement in symptoms with vitamin D supplementation [24]. The mechanism of this effect may be attributed to the role of vitamin D as an immune modulator and anti-inflammatory agent, reducing the release of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, and stimulating the function of T regulatory cells [25, 26]. It also affects the gut microbiome [27]. In contrast, a recent randomized, double-blind, placebo-controlled trial showed no advantages in administering vitamin D to patients with IBS, even those with vitamin D deficiency [28]. Long-term follow-up of patients treated with vitamin D supplementation in IBS has not been reported [29].

The gut microflora is a contributing factor in the pathogenesis of IBS. It is affected by gastroenteritis, surgery, and antibiotics, precipitating IBS symptoms. The fecal flora of patients with IBS is different from healthy controls, showing reduced numbers of coliforms, lactobacilli, and bifidobacterial spp. [30]. The use of nonabsorbable antibiotics has been suggested to target alterations in the microbiota in IBS [31]. Rifaximin is a broad-spectrum nonabsorbable antibiotic that appears beneficial after two weeks of treatment, alleviating abdominal pain and bloating and relieving diarrhea [32]. This effect appears to decrease at ten weeks of follow-up; however, repeat treatment with rifaximin showed improvement of symptoms [33, 34].

Probiotics are living organisms that comprise different types of streptococci, lactobacilli, bifidobacteria, and yeast. Probiotics seem to be effective in relieving IBS symptoms and stabilizing immune dysregulation [35]. However, their long-term effects remain uncertain [36]. Two meta-analyses assessing probiotics in IBS showed that long-term use of probiotics is associated with reduced efficacy and no improvement in IBS symptoms [37, 38].

Abnormal gastrointestinal motility is an essential pathophysiological mechanism in IBS, with increased motility reported in IBS-D and decreased motility in IBS-C [39]. Antispasmodics reduce gastrointestinal contractility by acting on the gastrointestinal smooth muscles. A meta-analysis assessing IBS symptoms using antispasmodics compared with placebo showed a short-term benefit [40]. Peppermint oil acts as an antispasmodic, anti-inflammatory, serotonergic, and opioid agonistic property. It has a significant benefit over placebo [41]. However, the most prolonged follow-up period in these trials was 15 weeks.

Intestinal secretagogues regulate intestinal water and electrolyte transport. Linaclotide and Plecanatide are agonists of the luminal receptor guanylyl cyclase C, which activates apical CFTR chloride channels via cGMP production [42]. Linaclotide improves stool frequency, ease of defecation, and symptoms, such as abdominal pain, discomfort, and bloating in 33% vs. 14% [43]. Lubiprostone activates type 2 chloride channels in enterocytes. A study of 1,171 patients showed that its use led to the relief of symptoms in patients with IBS-C over 12 weeks [44]. Tenapanor inhibits gastrointestinal sodium-hydrogen exchanger three that increases the fluid volume of stool by reducing sodium absorption, improves stool pattern, and reduces abdominal pain. In a study of 356 patients, tenapanor improved stool frequency and abdominal symptoms over 12 weeks [45].

Opioid receptors are located throughout the paleospinothalamic pathway from the cerebral cortex until the peripheral myenteric and submucosal plexus and play a role in the gut-brain axis. Moreover, opioid receptors are responsible for chronic pain [46]. Morphine decreases lower esophageal sphincter pressure, delays gastric emptying, and relieves pain through its function in the CNS. Fedotozine has the same antinociceptive qualities as morphine, increasing bowel motility [46]. Different opiates can treat diverse types of IBS. In IBS-D, loperamide, which induces constipation, reduces episodes of incontinence [47]. In IBS-C, fedotozine, a K-receptor agonist, was suggested to alleviate symptoms of abdominal pain and bloating [48], but clinical trials have shown a lack of efficacy [49]. Phase II clinical trials showed that asimadoline, a selective K-receptor agonist, was beneficial in IBS-D [49, 50].
5-HT receptors play a role in the gut-brain axis due to their effect on the CNS and ENS. The enteric system can cause bowel contractions or smooth muscle relaxation [51]. 5-HT3 receptor antagonists alleviate IBS-D, and 5-HT4 receptor agonists assist IBS-C. 5-HT3 receptor antagonists, such as alosetron and ondansetron, delay colonic transit time in patients with IBS. Stasi et al. and Johanson relieve symptoms in patients with IBS-D. 5-HT4 agonists, such as tegaserod and prucolapride, increase colonic transit time and improve symptoms in up to 70% of patients [51, 52].

2.2. Nonpharmacological Treatments. IBS treatment is challenging for both patients and caregivers due to the lack of curative treatments and its multifactorial pathophysiology [14–17, 53]. The relationship of patients with their health care provider is essential to optimize patient care in IBS and improve the patients’ quality of life [54]. Due to its chronic nature, patient education is essential for IBS management. Structured patient education was beneficial in improving symptom severity and quality of life [55]. Both multidisciplinary patient education and nurse-based education were effective in improving symptoms [56]. Education using digital methods can reduce health expenses. Moreover, webinars prepared using dietary management guidelines improve patient knowledge and are cost-effective [57].

Psychological therapies, including cognitive-behavioral therapy (CBT), are used in patients with IBS. Sustained stress can persistently increase central stress circuits’ responsiveness and vulnerability to functional disorders. Studies showed a relationship between IBS and stressful or traumatic life events and comorbidity with anxiety disorders [58]. In a Cochrane review of 25 controlled trials, CBT, stress management, relaxation therapy, and interpersonal psychotherapy were superior to usual care. Studies comparing interpersonal therapy with placebo and one study comparing CBT with placebo showed significant improvement. A systematic meta-analysis of 41 RCTs of CBT showed that gut-directed hypnotherapy, dynamic psychotherapy, and group therapies effectively alleviated IBS symptoms. In patients with refractory symptoms, only CBT and gut-directed hypnotherapy were effective [59]. The sustained benefits of these treatments remain unelucidated. Studies with up to 15 months of follow-up showed a loss of treatment effect over time [60].

Patients with IBS report symptoms related to food ingestion, making dietary approaches attractive [61]. Patients with IBS show higher small intestinal bacterial overgrowth (SIBO) associated with IBS symptoms [62, 63]. A reduction in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP), found in foods containing lactose and fructose, which are poorly absorbed, is beneficial in IBS [62, 64]. A high FODMAP diet worsened the symptoms of IBS [65]. Restriction of FODMAP reduces bacterial count and changes intestinal microbiome [66]. A randomized controlled crossover trial showed reduced symptoms in half of the patients [66, 67]. The long-term effects of low FODMAP diets (LFD) on symptoms and the microbiome are yet to be determined [61, 68, 69].

Both soluble and insoluble fibers can alleviate the IBS symptoms. Insoluble fibers have a laxative effect by increasing fecal mass, secretion, and peristalsis via mechanical stimulation of the colonic mucosa. Short-chain fibers can be fermented by increasing the colonic biomass and fecal mass, altering the microbiota composition, and affecting the oronasal transit time. Fermentation of by-products lowers the intestinal pH, affecting the gastrointestinal neuroendocrine system. Soluble viscous long-chain dietary fibers are minimally fermented and form a gel that normalizes stool form [70]. A meta-analysis of 11 RCTs showed a significant improvement in the global assessment of IBS symptoms. However, no improvement in abdominal pain, severity risk scores, and quality of life scores have been demonstrated [71]. There appears to be no long-term follow-up data on treatment with soluble fibers.

Acupuncture stimulates the somatic nervous system and vagus nerve, causing alterations in intestinal motility [72]. Several systemic reviews failed to show a significant benefit compared to sham treatment but showed improvement related to a placebo effect [73–75]. In contrast, a meta-analysis of six randomized controlled trials showed significantly favorable outcomes of acupuncture compared to placebo [76]. A study evaluating acupuncture in the primary care setup alleviated IBS symptom severity score (IBS-SSS) for up to 12 months duration [77], but not sustained for 24 months [78].

Taken together, the major drawback of both pharmacological and nonpharmacological therapies is the lack of sustainability of their effects [14–17, 79, 80].

Guidelines use a stepwise approach for the treatment of IBS [13]. Step 1 comprises behavioral modification, diet therapy, and gut-targeted pharmacotherapy for four weeks. For nonresponders, step 2 suggests a combination of several mechanism-based gut-targeted agents and psychopharmacological agents and psychotherapy for four weeks. For nonresponders, step 3 comprises combined gut-targeted pharmacotherapy, psychopharmacological treatments, and a more specific psychotherapy [13]. Overall, the treatment of IBS remains a challenge, and improving the quality of life is difficult in many chronic patients.

3. The Role of Chronobiology in the Pathogenesis of IBS

The circadian clock is a regulator of multiple biological processes [81]. The endogenous clock is a highly conserved timekeeper that supports the daily cycle of physiological processes and maximizes the proper functions of biological systems. Circadian rhythms coordinate cellular reactions, organ function, and body homeostasis [82]. In the intestine, the circadian rhythm regulates the transcriptional and translational feedback loops that culminate in the rhythmic expression of a set of clock genes and related hormones [83]. The suprachiasmatic nucleus and peripheral core molecular clocks oscillate every 24 h, regulating the periodic activity of the gut endocrine, immune, and nervous systems controlling intestinal functions and transit. Circadian rhythms are linked to energy balance regulation and nutrition. The circadian clocks showing lowered nocturnal activity regulate the motility of the colon. Healthy humans have
normal bowel motility following awakening or a meal, with minimal activity during the night [83].

The circadian clock regulates several potential mechanisms underlying IBS. Disturbed gut circadian rhythms lead to constipation and IBS [83]. Microbes contribute to the maintenance of clock function [82]. Disruption of the circadian system alters the microbiome to alter host metabolism, energy homeostasis, and inflammatory pathways [84]. Circadian-controlled dynamic neuroimmune routes in the gut regulate the association between innate immune protection mediated by IL-22 and food absorption [85].

Circadian rhythms are also associated with diet. The host circadian rhythm and timing of feeding are cross-regulated, hence controlling multiple physiological functions, including host immunity and metabolic health [86]. Diurnal shifting of the diet-microbiome-host immune axis is relevant to the gut, nervous system, and endocrine physiology. They also impact the gut-brain interactions [86, 87]. A high-fat diet disturbs the circadian rhythm of the microbiome. Morning soy protein intake led to greater microbiota diversity and a decrease in the cecal pH resulting from the production of short-chain fatty acids in mice [88]. The circadian hormone melatonin can improve lipid metabolism by reprogramming the gut microbiota, exhibiting rhythmicity in a light/dark cycle. Melatonin regulates the gut microbiota circadian rhythms in mice [89].

In preclinical models, poor sleep altered the gut microbiome and fecal metabolome, identifying sleep disruption-sensitive bacterial taxa and metabolites [90]. In humans, the day and night cycles underlie the function of the central and gut clocks. Sleep disorders are associated with diet and IBS [91]. Short sleep durations disrupt the intestinal gut microbiota, contributing to an inflammatory state, intestinal dysmotility, and alterations in metabolism associated with shift work [92]. In a clinical trial of healthy volunteers, rotational day and night shift work disturbed the circadian rhythm, altering the abundance of gut microbiota, which may be associated with intestinal pathology [93].

A clinical trial of 170 volunteers determined the association between the CLOCK 3111T/C single nucleotide polymorphism and the Period3 (PER3) variable-number tandem-repeat polymorphism with morning gastric motility. The data showed that minor polymorphisms of the circadian rhythm genes CLOCK and PER3 are linked to poor morning gastric motility [94]. Participants with the CLOCK C allele showed a significantly lower frequency of gastric motility.

While chronobiology plays a role in the pathophysiology of IBS, chronotherapy, the provision of therapies based on the circadian rhythm, has not yet been applied to optimize treatment in these patients.

4. Using the First-Generation Artificial Intelligence Systems in IBS

Selection of the treatment is a challenge in patients with IBS due to the low response rate and dynamic nature of this relapsing and remitting syndrome [13].

First-generation gastroenterology-directed AI systems may assist in diagnosing, selecting appropriate therapies, and predicting disease prognosis and outcome of diseases [95, 96]. Most first-generation systems evolve from the notion of collecting big datasets for identifying patterns and implementing them to improve diagnosis and management. The diagnosis of many gastrointestinal conditions relies on image-based procedures, making AI systems ideal for increasing the accuracy of diagnosis using AI-assisted image analysis. AI can also assist in integrating genomic, epigenetic, and metagenomic data, improving the accuracy of diagnosis of gastrointestinal malignancies [97–99]. AI platforms can assist in managing relapsing and remitting diseases, such as IBS, inflammatory bowel disease, or peptic ulcer bleeding, as a complex neural network may formulate models to predict disease outcome and enhance treatment efficacy [96]. However, while treatment algorithms are more straightforward for the last two examples, enabling closed-loop systems in designing large dataset-based treatment schemes, the case is different for IBS.

Being a multifactorial syndrome and the lack of biochemical or image-based criteria for establishing diagnosis limits the incorporation of first-generation AI platforms in diagnosing IBS. Patients with IBS show low response rates to most therapies, require combination therapies, and show dynamic changes in disease patterns and severity over time, which are obstacles for most currently developed AI systems [95].

Psychological and biological disease models assist in the diagnosis of IBS. A symptom network and an adaptive network may assist in specifying and covariation of symptomatology [100]. Only the adaptive network model, which assumes that a network of biological mechanisms has emergent properties and can exhibit adaptation, was able to explain the covariation of somatic symptoms of IBS. A recent study determined the prediction of symptoms with pathology in patients with IBS. It showed that network connection strengths vary with pathology, supporting the notion that functional disorders are associated with network adaptation. Using a machine learning analysis on surveys from 1,751 people reporting IBS, fibromyalgia, and chronic fatigue syndrome identified eleven symptoms. The strength of the associations between clusters varied due to symptom frequency. The data suggested an ability to diagnose IBS based on clusters of symptoms. The results imply that the body uses complex adaptation and that functional disorders, such as IBS, result when maladaptive changes occur to rules that generally improve adaptation [100].

A recent trial determined the feasibility of quantifying small bowel motility using magnetic resonance imaging (MRI) in a larger population with a spectrum of GI conditions with impaired small bowel motility. Motility quantitation showed marked differences in the motility of the terminal ileum in patients with small bowel Crohn’s disease but not in patients with IBS [101].

Dietary adherence to a low FODMAP diet (LFD) is difficult. Heali is an AI-based dietary application designed to improve adherence to LFD, IBS symptoms, and quality of life outcomes. In a trial of 58 patients with IBS, the reduction
in symptom severity score was 24% greater in the study group than in the control group, although this difference was not significant [102].

In summary, the attempts to implement first-generation AI systems in patients with IBS did not lead to a validated diagnostic or therapeutic scheme that could assist in managing IBS in most patients.

5. Establishing a Second-Generation AI System to Improve the Management of Patients with IBS

The second-generation AI system provides a comprehensive solution for the three gaps in the management of IBS in patients. These include difficulties in diagnosing, treating, and monitoring these patients.

Table 1 summarizes some of the barriers in diagnosing, treating, and monitoring patients with IBS and the solutions offered using second-generation AI systems.

5.1. Use of a Second-Generation System to Improve IBS Diagnosis. The lack of validated tests for IBS diagnosis makes it challenging to design diagnostic algorithms. The second-generation system can select subgroups of patients that require further evaluation by colonoscopy or motility tests. The system also assists in searching datasets for identifying costly patients who do not respond to therapies and may benefit from second-generation algorithm-based therapies [95, 103]. This subgroup of patients is a significant burden on the health care system, and targeting them may alleviate the burden on caregivers and payers while improving their overall quality of life and response rates of patients with IBS.

5.2. A Patient-Tailored Approach for Improving Response to Therapy in IBS. The Digital Pill comprises any type of pharmacological therapy for IBS regulated by a second-generation algorithm [104] and improves therapies’ effectiveness and patient adherence [95, 105, 106]. The patient receives the medication as prescribed by the physician with an app that has predefined therapeutic regimens dictated by the physician.

The Digital Pill system for patients with IBS is being developed in a stepwise manner comprising three levels [104]. In the first level, an application is provided to patients and reminds them of the dose and time of administration of the selected treatment. Physicians enter into the application ranges of dosages and administration times of each drug and other interventions within the approved ranges [104]. The embedded algorithm introduces variabilities in dosing and times within predetermined ranges [95, 104]. Treatment regimens based on aperiodic routines of taking the medication at irregular intervals and strengths may improve responsiveness [87, 103, 105, 107–113].

In contrast to first-generation systems, the second-generation system provides a means for a continuous dynamic feedback loop that accounts for changes in patient outcomes, response to therapy, disease manifestations, and environmental factors [95]. The system can also be applied to nonpharmacological therapies and assist in improving the response to sports activities, diets, and other interventions in patients with IBS [87, 103, 104, 113–115].

The Digital Pill is a simple system that can improve the response to the currently used treatment methods in patients with IBS. It may overcome drug resistance in multiple chronic diseases and conditions, including inflammatory bowel diseases [111], arthritis [111], epilepsy [116], cancer [108], metabolic diseases [87], obesity [113], pancreatitis [110], microbiome-based disorders [117], infections [109, 118], microtubule-linked disorders [119–121], chronic pain [112], rare diseases [103], and chronic inflammation [122].

Variability is inherent to biological systems and responses to medications. It partially underlies the partial or complete loss of response to chronic drugs [123–125]. Studies showed a high degree of inter- and intrapatient variability for drug metabolism, pharmacodynamics, and drug responsiveness [104–106, 126, 127]. Regular administration of a daily dose at fixed times is associated with drug resistance [107], while drug holidays can improve it [105, 128].

The first level of the Digital Pill can assist in overcoming the partial or complete loss of the effect of chronic drugs used for IBS. While first-generation platforms suffer from a lack of adherence by patients, the second-generation system is aimed at improving clinically meaningful outcomes, ensuring improved adherence [95]. Improving the clinical symptoms when using the application ensures a continuous motivation for using the drug based on the regimen provided by the application.

The second level of the system includes a closed-loop system directed to alter the variability in dosages and administration times based on the response to therapy. It implements chronobiology variables for the pharmacotherapy of IBS. The system receives feedback from the patient and caregivers and implements data collected from other patients. Endpoints for the algorithm are predefined clinical outcomes and are patient-tailored [104]. The algorithm alters the variability in dosing and times of administration of drugs based on the patient’s clinical response. The system continuously personalizes each subject’s therapeutic regimen based on predefined outcome measures [95, 104].

At the third level, the system implements variability signatures relevant to the disease into the treatment algorithm [95, 104]. Examples are evident for other chronic diseases: variability in cytokine profiles in patients with inflammatory bowel diseases or arthritis [111], heart rate variability in patients with chronic heart diseases [105], and electroencephalogram-derived variability data in patients with epilepsy [116]. For patients with IBS, implementing inherent variabilities associated with the immune system (e.g., cytokine patterns), microbiome-signatures, patterns associated with the autonomic nervous system (e.g., heart rate variability), and motility test-derived parameters can improve the therapeutic regimen and hence the clinical outcome [104]. The algorithm can select the appropriate variability patterns in a patient-tailored way by continuously comparing inputs of different variability signatures on the output of the therapeutic schedule in a way that adapts itself to the selected outcome (e.g., improvement in bloating, pain, and diarrhea).
Dysregulation of the brain-gut axis is associated with IBS. A recent clinical trial applied multivariate pattern analysis to identify an IBS-related morphometric brain signature that could serve as a biomarker. Parcellation of 165 cortical and subcortical regions used FreeSurfer and Destrieux and Harvard-Oxford atlases. The study used a training set of 160 participants consisting of 80 healthy controls and 80 patients with IBS for modeling. The predictive accuracy of the classification algorithm was 70% based on regional brain morphometry. While the algorithm’s accuracy may be insufficient, it suggests the potential of using brain-derived signatures to improve the algorithm [129].

The second-generation system has several advantages for patients with IBS and can overcome several obstacles first-generation systems face. The system evolves from an $n = 1$ concept, ideal for patients with IBS for whom large, validated datasets are not always available. The marked phenotypic differences among patients with IBS make it inappropriate to “force averages” resulting from accessible datasets on an individual patient [130]. The system continuously adapts the therapeutic schedule to the dynamicity of the symptoms, which is common in patients with IBS, and adapts itself to alterations in the degree of responsiveness to therapies [104].

Figure 1 demonstrates a schematic presentation of a second-generation artificial intelligence system for improving diagnosis, treatment, and follow-up of patients with irritable bowel syndrome (IBS). Data is inserted for a patient with a gastrointestinal disorder to improve diagnosis and identify optimal treatment regimens with continuous feedback, modifications, and better monitoring.

### Table 1: Overcoming significant gaps in the diagnosis, treatment, and monitoring of patients with IBS using second-generation artificial intelligence systems.

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Multifactorial nature of IBS</td>
<td>(i) A digital system that collects and integrates different datasets</td>
</tr>
<tr>
<td>(ii) Lack of validated tests</td>
<td>(ii) Identification of patient subgroups that require further evaluation by colonoscopy and motility tests</td>
</tr>
<tr>
<td></td>
<td>(iii) Identification of patients who do not respond to treatment and may cause high health care costs</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>(i) Low response rates</td>
<td>(i) A digital system with continuous dynamic feedback helps improve patient adherence, management of symptoms, and adaptation to the changing nature of the disease</td>
</tr>
<tr>
<td>(ii) Require combination therapy</td>
<td>(ii) Provides a valid tool for caregivers to follow patients’ adherence and responsiveness</td>
</tr>
<tr>
<td>(iii) Changes in IBS pattern over time</td>
<td>(iii) The dynamic nature of the artificial intelligence system helps both patients and caregivers to tailor the relevant follow-up variables</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>(i) Chronicity imposes a health care challenge to monitor patients</td>
<td>(i) A tool in the digital system to collect data of symptoms, the effectiveness of therapy, and side effects</td>
</tr>
<tr>
<td>(ii) Changes in IBS pattern over time</td>
<td>(ii) Provides a valid tool for caregivers to follow patients’ adherence and responsiveness</td>
</tr>
<tr>
<td>Monitoring</td>
<td></td>
</tr>
</tbody>
</table>

5.3. **Patient-Tailored Monitoring System for Patients with IBS.** The second-generation system provides a method to monitor patients with IBS based on a dynamic outcome approach, leading to improved care and saving costs [103, 131]. The application provides patients with a tool to collect data on their symptoms, effectiveness of therapy, and side effects. Physicians can adhere to the therapy and responsive-
6. Summary

Treatment of patients with IBS remains a challenge. The use of second-generation AI systems can provide an inclusive solution to improve the diagnosis and classification of patients for appropriate therapies. The system provides a tool for overcoming the loss of response to therapies, ensuring a sustainable effect and increased patient adherence while providing an outcome-based monitoring tool. Ongoing trials are aimed at validating the system in patients with IBS and enabling the upscaling of the algorithm.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>AI</td>
<td>Artificial intelligence</td>
</tr>
<tr>
<td>IBS-C</td>
<td>IBS with predominant constipation</td>
</tr>
<tr>
<td>IBS-D</td>
<td>IBS with predominant diarrhea</td>
</tr>
<tr>
<td>IBS-M</td>
<td>IBS with mixed bowel habits</td>
</tr>
<tr>
<td>IBS-U</td>
<td>Unclassified IBS</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>ENS</td>
<td>Enteric nervous system</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>GAD</td>
<td>Generalized anxiety disorder</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>CFTR</td>
<td>Cystic fibrosis transmembrane conductance regulator</td>
</tr>
<tr>
<td>cGMP</td>
<td>Cyclic guanosine monophosphate</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-Hydroxytryptamine</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive-behavioral therapy</td>
</tr>
<tr>
<td>SIBO</td>
<td>Small intestinal bacterial overgrowth</td>
</tr>
<tr>
<td>FODMAP</td>
<td>Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols</td>
</tr>
<tr>
<td>LFD</td>
<td>Low FODMAP diet</td>
</tr>
<tr>
<td>QOLS</td>
<td>Quality of life scores</td>
</tr>
<tr>
<td>IBS-SSS</td>
<td>IBS symptom severity score</td>
</tr>
<tr>
<td>PER3</td>
<td>Period 3</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
</tbody>
</table>

Data Availability

This is a review, and all data is available in PubMed.

Conflicts of Interest

The authors declare that they have no conflicts of interest. YI is the founder of Oberon Sciences.

Authors’ Contributions

Anat Hershko-Moshe and Yaako’v Hasin contributed equally to this work.

References


Y. Ilan, “Microtubules: from understanding their dynamics to using them as potential therapeutic targets,” *Journal of Cellular Physiology*, vol. 234, no. 6, pp. 7923–7937, 2019.


