Richard W. McCallum, MD, FACP, FRACP (Aust), FACG, AGAF

Current Treatment Strategies for Irritable Bowel Syndrome

Pratik Naik

Richard W. McCallum

Irritable bowel syndrome (IBS) is a functional bowel disorder which affects 11% of the world's population. IBS is accompanied by significant socioeconomic burden, and a lack of recognition of the condition leads to many patients left undiagnosed. The pathophysiology of IBS is not well understood but new concepts are emerging. Treatment of irritable bowel has always been challenging and focuses on addressing abnormal stool frequency, abdominal pain and the psychological state. In this article, we provide an update on IBS therapies newly approved by the Food and Drug Administration (FDA), suggest strategies for incorporating the spectrum of the medications that are already being utilized for specific IBS patient settings and also preview new therapeutic directions.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain associated with a change in bowel habit. More specifically, the Rome IV criteria for IBS state that patients should have recurrent abdominal pain for at least one day a week in the last three months associated with at least two of the following: pain related to defecation, onset of pain associated with a change in frequency of stool or onset of pain associated with a change in form of stool (Bristol stool scale criteria).[1] These symptoms must be present for at least six months before diagnosis, however they may be present for years prior to the patient's initial evaluation. Additionally, clinical criteria, such as symptoms exacerbated by stress, symptoms occurring during the day and not while asleep, incomplete evacuation and bloating and distension, can be utilized in making the diagnosis of IBS.

In the United States, the prevalence of IBS approaches 16% (45 million) of which 70-80% are

Pratik Naik, MD, GI Motility Fellow and Richard W. McCallum MD, FACP, FRACP, FACG, AGAF, Founding Chair, Department of Medicine, Director, Center for Neurogastroenterology and GI Motility, Texas Tech University, Paul L. Foster School of Medicine El Paso, TX

women.[2,3] IBS can be diagnosed in all age groups[4] however roughly 50% of patients with IBS report their first symptoms before the age of 35 years.[5] These symptoms affect quality of life and the patients have many absences from work.[3] However, there is a lack of recognition of the condition and up to 75% of patients either do not seek medical attention or are not formally diagnosed.[2] There are often concomitant entities, specifically fibromyalgia, chronic fatigue syndrome, chronic migraine headache, interstitial cystitis and temporomandibular joint dysfunction, that can co-exist in half of IBS patients and provide a clinical clue to consider IBS as an underlying diagnosis.[6,7]

Improving a patient's quality of life is the mainstay of treatment. Establishing physician rapport, patient education on IBS and empowering them to accept some responsibility for their care are key as well. Non-pharmacological approaches such as stress management, psychotherapy, behavioral modifications and focus on diet have been shown to improve symptoms and should be sustained long term. In this article we describe the new IBS therapies as well as suggest strategies for incorporating them into the spectrum of the medications that already have been shown to be useful and focus on specific patient challenges.

IBS with Diarrhea (IBS-D)

IBS-D accounts for approximately one third of all IBS patients and affects roughly the same number of men and women. Anti-diarrheal agents such as loperamide, in previous randomized controlled trials (RCTs), have failed to demonstrate benefit in relieving global symptoms of IBS, specifically the abdominal pain.[8, 9] However, the fear of fecal incontinence accompanying the urgency of the diarrhea means that loperamide can be efficacious for reducing stool frequency in specific settings such as maintaining daily work schedules, traveling, social outing and stressful events.[10]

Available New Therapies for IBS-D

Rifaximin (Xifaxin)

The FDA approved rifaximin for treatment of IBS-D in May, 2015. Rifaximin is a minimally absorbed antibiotic whose mechanism of action is inhibiting bacterial protein synthesis and modulation of intestinal microbiota that are contributing to a microscopic inflammatory process in the bowel.[11] There were two TARGET (Targeted non-systemic Antibiotic Rifaximin Gut selective Evaluation Treatment of non-constipated IBS) studies where patients were treated with rifaximin 550mg three times daily for 14 days vs. placebo and followed for a 10 week treatment-free observation period. The primary endpoint was adequate relief of IBS signs and symptoms. This was accomplished significantly more in the rifaximin group than in the placebo group during the four weeks of observation after treatment in the two studies combined (40.7% vs. 31.7%, $P<0.001$). In an assessment of the composite end point of abdominal pain or discomfort and loose or watery stools, significantly more patients in the rifaximin group than in the placebo group had relief during the evaluation period (46.6% vs. 38.5%, $P=0.04$, in TARGET 1; 46.7% vs. 36.3%, $P=0.008$, in TARGET 2).[12] Since IBS is a chronic disease, assuming that only two weeks of therapy is going to produce sustained symptom relief was a concern raised by the FDA ultimately leading to an additional study aptly called TARGET 3. In this trial, 2579 patients initially treated with open labeled rifaximin were then followed for 18 weeks and patients received re-treatment in a double blinded fashion if they relapsed. Here, the 636 patients who experienced recurrent IBS symptoms were randomized to receive rifaximin 550mg TID vs. placebo for two weeks followed by a four week treatment-free observation period. The percentage of responders in the retreatment phase was again statistically significant for rifaximin 550 mg vs. placebo-treated patients (37% vs. 29%, $p=0.04$).[12]

The adverse events observed during these trials, nausea (3%) and elevated alanine aminotransferase (2%), were infrequent.[13] There was no increased risk of infections, including Clostridium difficile infection, and no substantial differences in any adverse events vs. placebo.[14] The FDA recommends evaluation for C. difficile if there is no improvement or worsening of diarrhea after treatment with rifaximin and cautions use in patients with severe liver impairment (Child-Pugh Class C) or with concomitant administration of drugs that are P-glycoprotein (P-gp) inhibitors (e.g. cyclosporine) due to increased systemic exposure to rifaximin.[13]

Eluxadoline (Viberzi)

The FDA approved eluxadoline for treatment of IBS-D in May, 2015. Eluxadoline is a μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist and has minimal absorption. This agent binds to peripheral opioid receptors in the gastrointestinal (GI) tract resulting in

slowing of GI motility and decreasing gut secretions. However, an additional unexpected mechanism was recognized. Eluxadoline was shown to decrease the sensitivity of afferent neurons (in the submucosa) to pain thus reducing visceral hypersensitivity, a local gut effect, with no central nervous system (CNS) involvement.[16,17] Two double-blinded, placebo-controlled clinical trials were conducted in which 2,427 patients were randomly assigned to receive eluxadoline (at 75 mg or 100 mg) or placebo twice daily (BID) for 26 weeks in both studies. Significantly more patients treated with eluxadoline 100 mg BID vs. placebo (33% vs. 20 %; $p< 0.001$) experienced improvements in diarrhea and abdominal pain for at least 50% of the trial period. This response was noted within the first week of initiating therapy.[17]

The most common side effects were constipation (8% vs 3% placebo), nausea (7% vs 5%) and abdominal pain (7% vs 4%). Upper abdominal pain attributed to sphincter of Oddi spasm was observed in 0.8% of the patients and was more likely to occur in patients with prior cholecystectomy. The presence of opioid receptors in the sphincter of Oddi could contribute to this observation. These symptoms were usually induced within the first two weeks of treatment and resolved upon discontinuation of the drug.[17] In addition, there was a rare occurrence of pancreatitis (less than 0.3%) not associated with sphincter of Oddi spasm and the majority of cases were related to excessive alcohol use. Because of this finding it is recommended that patients with history of chronic pancreatitis or currently consuming at least three or more alcoholic beverages daily do not receive this agent.[16]

The current recommended dose for eluxadoline is 100mg twice daily. The reduced dose, 75 mg twice daily, is initially appropriate for patients post cholecystectomy, those who were not able to tolerate the 100 mg dose, who are receiving concomitant OATP1B1 inhibitors (e.g. cyclosporine and gemfibrozil) or who have mild to moderate hepatic impairment. The use of this agent is not recommended if there is suspected mechanical gastrointestinal obstruction or severe liver impairment (Child-Pugh Class C).[16]

Alosetron (Lotronex)

Alosetron, a selective 5-HT_3 antagonist, was initially approved by the FDA in 2000 for the treatment of IBS-D in women only. Activation of 5-HT3 receptors leads to neuronal depolarization in enteric neurons which reduces visceral pain as well as colonic transit and inhibits GI secretions.[18] The drug was later withdrawn due to the serious adverse event of ischemic colitis (IC) and constipation. It was reintroduced in 2002 by FDA under a risk management program with a reduced dose (0.5-1 mg BID) for treatment of IBS-D in women only who were not responding to standard therapies.[19]

In randomized controlled trials (RCTs), alosetron improved abdominal pain and IBS-related global symptoms compared to placebo.[20] Post-marketing safety of alosetron under the risk management program (2002-2011) reported a low incidence of serious complication of constipation (0.25 cases/1000 patient-years) and ischemic colitis (1.0 case/1000 patient-years).[19] Constipation was dose dependent and noted in 29% of patients receiving the 1 mg BID dose compared to 11% in the 0.5 mg dose. The overall incidence of serious constipation was higher in elderly patients or patients taking additional medications that decrease GI motility. Alosetron should be discontinued in patients who develop constipation and it can be restarted under supervision of a prescriber after constipation resolves.[25] Alosetron should not be used in patients with history or have high risk for IC. It is also contraindicated in patients with suspected intestinal obstruction, inflammatory bowel disease (IBD), diverticulitis and severe hepatic dysfunction (Child- Pugh Class C).[21]

IBS with Constipation (IBS-C)

IBS-C accounts for approximately one third of all IBS patients. Over the counter laxatives [polyethylene glycol (Miralax) and bisacodyl (Dulcolax)] can be useful short term in management of constipation in improving stool frequency. However, this type of long-term management does not provide adequate pain relief.

Available New Therapies for IBS-C

Linaclotide (Linzess)

Linaclotide has been approved to treat IBS-C and chronic idiopathic constipation since 2012. Linaclotide, a guanylate cyclase C (GC-C) receptor agonist, induces an increase in both intracellular and extracellular concentrations of cyclic GMP which stimulates secretion of chloride and bicarbonate into intestinal lumen by activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. This increases fluid in the intestine leading to an acceleration of colonic transit.[22] Based on data from

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animal models, linaclotide also was able to decrease abdominal pain through effects on afferent neurons in the gut wall.[22,23] In two phase III multicenter placebo-controlled RCTs, linaclotide significantly increased the frequency of complete spontaneous bowel movements and reduced abdominal pain for at least six of the 12 weeks compared to placebo (Trial 1: 33.6% vs 21%; Trial 2: 33.7% vs 13.9%).[24,25] In all three multicenter placebo-controlled RCTs, linaclotide was shown to be effective in reducing global symptoms of IBS-C.[20]

Linaclotide 290 mcg is taken once a day on an empty stomach for treatment of IBS-C. Recently a new formulation allows the capsule to be ground and given as a powder with apple sauce orally or through a feeding tube if swallowing problems are present. Diarrhea (20% vs 3% placebo) was the most common adverse reaction noted in trials. Severe diarrhea was reported in 2% compared to less than 1% in placebo group, and diarrhea resulting in discontinuation was 5% vs <1%. The majority of reported cases of diarrhea started within the first two weeks of the treatment and reduced with time.[22] Patients with known or suspected mechanical gastrointestinal obstruction or sudden change in clinical states are not appropriate candidates nor should the drug should be used in patients 17 years of age and younger.[23]

Lubiprostone (Amitiza)

Lubiprostone (Amitiza) 8 mcg BID was approved by the FDA in 2008 for the treatment of women with IBS-C. It activates type 2 chloride channels in small intestinal cells that promote chloride secretion in intestine.[26] These secretions soften the stool and increase colonic transit time, which promotes more complete spontaneous bowel movements. In two phase three RCTs, the percentage of overall responders based on patient-rated assessments of IBS-C symptoms was significantly more in patients treated with lubiprostone 8 mcg twice daily compared to those treated with placebo (17.9% vs. 10.1%, p=0.001).[27] The most frequent adverse events were nausea (8% vs 4%) and diarrhea (7% vs 4%). Long term safety, 36 weeks, and tolerability were assessed in an additional study; while not placebo controlled, 41% of patients dropped out due to lack of efficacy.[28]

Treatment Option for IBS-M

The prevalence of IBS-M is equal in both male and female. Abdominal pain remains a challenge for these patients and anticholinergics have been heavily utilized in their management. Hyoscamine, dicyclomine and chlordiazepoxide/clidinium bromide (Librax) are widely used to alleviate abdominal spasms and cramps associated with IBS as well as deceases GI motility and hypersensitivity.[29] Previous studies have shown limited evidence regarding long term efficacy in reducing global IBS symptoms and abdominal pain.[20] The most common side effects are anhidrosis, blurred vision, confusion, constipation, urinary retention, xerostomia and drowsiness attributed to anticholinergic effects.[18,20]

Available New Therapies for IBS-M

IBgard (Peppermint Oil)

IBgard, purified peppermint oil, reduces lower GI tract and colon motility by acting on intestinal calcium channels to relax smooth muscle within the GI tract.[30] It is a enteric-coated preparation permitting it to bypass the stomach and delivers peppermint oil to the small bowel allowing its effect to be maximal on the lower GI tract.[31] In a placebo-controlled, double-blinded RCT, 72 patients who met the Rome III criteria for IBS-M and IBS-D were randomized to receive IBgard 180mg TID vs placebo for 4 weeks. There was a significant reduction in the number of severe or unbearable IBS symptoms vs placebo (66% vs 42%, P=0.02) and reduction in severe or unbearable abdominal pain intensity vs placebo (79.4% vs 40.5%, P=0.01). The study also showed improvement in IBS global symptoms.[32] The mechanism of action, particularly for reducing pain, remains poorly defined.

Peppermint oil can also relax the lower esophageal sphincter, which can lead to symptoms of acid reflux when taken orally.[31] Enteric-coated preparations can eliminate this side effect. IBgard is an OTC medication; however, it should be used under physician supervision. It is not recommended in patients with IBS-C since constipation may be worsened.

Suggested Strategic Approaches Based on These New Therapies in IBS-D

1. Choice of Rifaximin

Rifaximin may be considered as a reasonable treatment of choice in the following clinical settings:

1. A patient with suspected post infectious (PI) IBS-D based on a very suggestive history of food poisoning, travel, military deployments etc.

2. Patients where the IBS presentation has been relatively short (< 5 years) with or without a typical post infection history.
3. Patients over 50 years of age where onset has been recent, this suggesting a higher likelihood for PI-IBS even when no specific event can be recalled.
4. Patients with IBS-D where gas, bloating and postprandial abdominal distension are prevalent suggesting a component of small intestine bacterial overgrowth (SIBO) as a manifestation of a recent GI infection or change in microbiota.

Rifaximin is not a stand-alone therapy. Patients seeing a gastroenterologist may already be following a low FODMAP (fermentable oligo-di-monosaccharide and polyol) diet and antidepressants but still have remaining symptoms. Here a course of rifaximin is a reasonable step in addition to the medications being received. Since it is a two-week regimen, there will be evidence for improvement within a short time.

Questions Remaining Regarding Rifaximin

1. How does one can explain the improvements in the abdominal pain with rifaximin when the rationale for its use is modulating microbiota? The current rationale is that its anti-inflammatory effects reduce microscopic inflammation in the gut wall including improving the concept of "leaky cell junctions", although there is no clear evidence of this to date.

2. Can two weeks of therapy sustain the reduction in abdominal pain? The FDA approval for rifaximin does allow for two more re-treatments to be given over time. The timing of the re-treatment course has been vague. The follow up in clinical trials was approximately five months so one could infer that re-treatment may be considered during that time frame for that subset of patients who initially achieved improvement and relapsed.

3. Will other agents be required to address pain relapses over greater time periods? Here there could be a role for antispasmodics as needed as well as assessing a role for tricyclic antidepressants in obvious stress related settings

4. Should patients completing a course of rifaximin then start probiotics in order to sustain a better microbiota environment? This has not been addressed in a study format. If gas and bloating were the deciding factors to initiate rifaximin initially then follow up probiotics seems reasonable

5. Can there be a profile of the best candidate? For the future, stool analysis of gut microbiota by polymerase chain reaction (PCR) may define particular subtypes who can be shown to be the best responders. This may be particularly relevant to explain a subset where effective pain reduction is being sustained.

2. Choice of Eluxadoline

The primary choice of eluxadoline may be considered in the following clinical settings:

1. Patients with IBS-D whose predominant symptoms are stool urgency and fear of having a "bowel accident" or actually experiencing intermittent fecal incontinence. The activation of opioid receptors in the gut wall makes sense in decreasing stool volume and transit as well as secretions. This is particularly relevant to morning diarrhea preventing timely arrival at work or leaving the home.

2. A history of chronicity (>5 years) would all favor eluxadoline since long term use has been studied (at least 1 year) and the FDA approval is also for chronic use since there was also an excellent safety profile.

3. Treatment with eluxadoline does not preclude concomitant therapies e.g. antidepressants, low FODMAP diets and addressing excessive bloating and gas to address the "peaks and valleys" during the course of chronic IBS where treatment with eluxadoline may be for months or years.

Questions Remaining Regarding Eluxadoline

There is a pressing need to clarify how the interactions of eluxadoline as an agonist of mu and kappa receptors and at the same time antagonizing delta receptors leads to decreased pain via afferent submucosal neurons. The role of kappa receptors still remains to be studied.

3. Choice of Alosetron

Alosetron could be a preferred consideration only in women with IBS-D where the diarrhea is such that

bowel movements and stool urgency with possible fecal incontinence are frequent and who have failed all other management strategies. As a part of a risk evaluation and mitigation strategy, patients and prescribers are required to enroll in a prescribing program and medication guide should be provided with each prescription.

Suggested Strategic Approaches Based on New Therapies in IBS-C

1. Choice of Linaclotide

Linaclotide should be considered as a treatment of choice in patients with predominant symptoms of constipation and abdominal pain. There are two main challenges:

1. The effects of the medication on abdominal pain can take up to 10 weeks to fully maximize presenting a challenge to keep patients motivated to take the medication with the possibility that a suboptimal pain relief will result. Anticholinergics may be needed as adjuncts to address pain during this time. A short acting agent such as hyoscyamine is preferred since long acting agents such as dicyclomine, librax and donnatal (belladonna alkaloids, phenobarbital) may worsen constipation. The good news for the patients is that increased frequency of stools occurs in the first 48 hours indicating to the patients that the drug is working (they are responders) and hence there is a high likelihood that abdominal pain relief should follow over the next few weeks

2. Initial diarrhea can be prominent and although the 290 mcg dose is recommended in IBS-C to achieve the long-term pain benefits, starting at 145 mcg and building up to 290 mcg will overcome the concern that diarrhea may result in a patient prematurely stopping the agent. An alternative strategy is to use 290 mcg every other day until the bowel adapts to the increase in luminal fluid and diarrhea is not a concern. This usually occurs over two to three weeks and then daily dosing can be initiated.

2. Choice of Lubiprostone

Lubiprostone was associated with mild to moderate nausea and vomiting (11%) which could be major limiting factor as well as the BID dosing and also the fact that it was only approved in women. There is also lack of evidence for long term safety and tolerability because the previous long term study had a high dropout rate (41%). Recently, Amitiza 24ug BID has been approved for opioid induced constipation. Hence in IBS patients taking opioids for other reasons e.g. back pain, neuropathy or headache, this high dose can be considered.

Strategies Approaches Based on These New Therapies in IBS-M

1. Choice of IBgard

IBgard is an OTC medication is only intended for use in D and IBS-M. It can be used as a short term adjunct when abdominal pain, spasm and discomfort are the main symptoms. However, more definition is required of the mechanism of action regarding reducing abdominal pain which is thought to be more colonic in origin yet the agent is largely presented to the small bowel. More RCTs are needed to evaluated long tern efficacy and tolerability. IBgard is an OTC medication but it should be taken under physician supervision.

Future Therapy Approaches

Role of Methanogens and Methane in IBS-C

Recently data has suggested an association of methane production with chronic constipation and IBS-D. The proposed mechanism is based on an animal model where methane was found to act as a neuromuscular transmitter and delayed intestinal transit.[33] Methanogens such as *Methaninobrevibacter smithii* have been found to have 80% – 100% colonization rate of the human colon by PCR techniques.[34]

In a study by Pimentel et al., methane production from a lactulose breath test showed 100% association with IBS-C patients and the prevalence of methane positivity was very low among patients with IBD and IBS-D. In that study, higher constipation severity scores were reported by subjects who produced methane.[35] However, this association with constipation is unclear as up to 50% of healthy individuals have been reported to be methane formers.[34] In addition, relying on the lactulose breath test is a major flaw since it is actually measuring colonic flora and not the small bowel flora as first assumed.

In a retrospective study, rifaximin and neomycin have shown promising results on methane eradication as

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measured by the breath test. Pharmacotherapy such as chloro/fluoromethanes, 2-bromo- and 2-chloro-ethane sulfonates also have been shown to block key reactions leading to methane biosynthesis. In a phase two trial, a modified-release formulation of lovastain lactone (SYN-010) was shown to act primarily in the intestinal lumen and reduced methane production by M. smithii with minimal impact on gut microbiome.[36]

Better understanding regarding the role of SIBO and microbiota in IBS patients is needed. Recent studies have demonstrated the utility of sampling small bowel contents and using PCR techniques in identifying differences in gut flora of IBS patients, specifically different phyla compared to healthy individuals. By using these techniques in the future, we may be able to identify subgroups of IBS patients who can be considered the most likely responders to targeted therapies.

Bile Acid Malabsorption

Bile acids (BA) are produced in the liver and have major roles in the absorption of lipids in the small intestine. Bile acid malabsorption (BAM) is estimated to occur in one third of the patients with IBS-D and up to 50% of the patients with functional diarrhea. SeHCAT (23-seleno-25-homotaurocholic acid, selenium homocholic acid taurine, or tauroselcholic acid) is a test used to diagnose BAM. This test is done by measuring retention of the SeHCAT by external scintigraphy one week after administration of a gamma-emitting synthetic bile acid and less that 15% retention after seven days is considered abnormal. In a systemic review in patients with IBD-D, BAM was noted as severe in 10%, moderate in 32% and mild in 26%.[37] The bile acid binder cholestyramine has been shown to improve BAM and potentially reduce diarrhea.

TAKE HOME MESSEGES

In this article we review current pharmacotherapy for all IBS subtypes. Treating IBS remains daunting for clinicians: abdominal pain and abnormal bowel function are dual challenges. In fact the statement is often made that the true measure of the skill of a gastroenterologist is how well he or she can treat patients with IBS in their practice. This article emphasizes the background and evidence for new pharmacotherapies now available to practicing gastroenterologists and primary care physicians and also proposes treatment strategies in specific patient settings. It also reminds us that IBS is a chronic entity and our goals are to minimize bad days and maximize good days and improve quality of life. Physician rapport and trust is key. It all begins with actually telling patients their diagnosis: you have irritable bowel syndrome. There are no stand-alone approaches. Current therapies as well as the new agents reviewed are integrated into the setting of addressing stress with antidepressants (e.g. tricyclics), psychological counseling and holistic approaches including relaxation techniques while always focusing on the role of diet. Evolving therapies and concepts regarding biomarkers particularly related to bile acid malabsorption and changes in gut microbiota specifically methanogens are also reviewed. The future will be more targeted therapies but this will also rely on unraveling an entity which will remain poorly understood until the big umbrella term of "IBS" can be replaced by describing entities based on specific mechanisms and pathology. ■

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Answers to this month's crossword puzzle:

1 C	H	2 O	L	3 A	N	4 G	I	5 T	I	6 S	■	7 E	M	8 S
Y	■	B	■	I	■	N	■	O	■	G	■	X	■	T
9 S	T	E	A	R	10 I	C	■	11 R	U	P	T	U	R	E
T	■	T	■	■	N	■	■	S	■	T	■	D	■	R
12 I	D	I	O	13 P	A	T	14 H	I	C	■	15 H	A	L	O
C	■	C	■	A	■	■	M	■	■	16 I	■	T	■	L
■	■	17 H	18 E	L	I	19 C	O	B	20 A	C	21 T	E	22 R	■
23 O	D	O	R	■	■	R	■	■	24 D	E	R	■	25 E	X
R	■	26 L	A	27 B	■	28 U	R	29 S	O	D	I	30 O	L	■
I	■	I	■	I	■	X	■	O	■	■	■	S	■	■
31 F	E	C	A	L	■	■	32 P	R	U	33 R	I	T	I	S
I	■	A	■	34 I	35 P	■	■	T	■	E	■	O	■	■
36 C	Y	C	L	A	S	37 E	■	■	38 S	T	A	S	I	39 S
E	■	I	■	40 R	A	T	■	41 D	■	C	■	I	■	O
42 S	A	D	■	Y	■	43 C	I	R	R	H	O	S	I	S