Treatment related risk, benefit, and access in functional GI and motility disorders

The experience of the IBS community with the drug alosetron and what it has taught.

International Foundation for Functional Gastrointestinal Disorders

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The process of drug development, review, delivery, and use is one that involves many stakeholders, including industries, regulators, physicians, and patients. All play roles that influence treatment outcomes. The illness experiences and perceptions of patients are key components to understanding a disease and providing safe and effective treatments. Looking at the experience of the IBS community with the drug alosetron as an example, this article reflects upon how treatment delivery can break down, and actions that can help ensure that safer, effective, treatments are made available to patients in need.

"In the U.S. drug safety system, in both the preapproval and the post marketing setting, the risk-benefit analysis that currently goes into regulatory decisions appears to be ad hoc, informal, and qualitative."

Introduction

The International Foundation for Functional Gastrointestinal Disorders (IFFGD) has been tracking, for over two decades, the needs of patients, both anecdotally and systematically. The needs of patients with functional gastrointestinal (GI) and motility disorders have not changed during that time.

The message continues to resonate that the severity of patients' symptoms is underestimated making it difficult for the treatment needs for these chronic disorders to be fairly assessed and adequately addressed.

Irritable bowel syndrome (IBS) is the most studied of these GI disorders. However, the burden of disease for patients with other functional/motility disorders such as gastroparesis, dyspepsia, pseudo-obstruction, or cyclic vomiting syndrome carries the same frustrations and challenges with getting accurate and timely diagnoses, effective treatments, and satisfactory care.

Functional GI and motility disorders (FGIMDs) are remarkably common in the general population. Prevalence figures vary, but it is safe to say that one in four Americans is affected by these disorders.[1,2] However, the conditions lack physical markers on which to base a diagnosis or measure severity. Consequently, this patient community has had to overcome significant obstacles to legitimize their suffering, which has played out on a number of different levels with various stakeholders.

Decisions made by the Food and Drug Administration (FDA), along with the pharmaceutical and healthcare industries, have impacted access to treatment for these patients. They also have prompted more research into areas of risk/benefit, efforts to define severity, and the development of endpoints and Patient Reported Outcomes.

This is a community of patients that has been disproportionately impacted over the past decade by risk management programs. We have seen a limited access program attached to cisapride (used to treat severe refractory reflux disease, gastroparesis, and pseudo-obstruction), the withdrawal of tegaserod (used to treat IBS with constipation), and the voluntary withdrawal of alosetron (used to treat IBS with diarrhea). Alosetron (Lotronex®) was subsequently reintroduced with a Risk Management Program (RMP) designed to mitigate serious outcomes of the adverse events, but physician enrollment in the RMP, and patient awareness of it as a treatment option, are both low.[3,4]

Decisions made by regulators are intended to protect patients and improve outcomes. But as with many broadly impacting decisions, there may be unintended consequences. It is important to recognize those consequences, and to learn from them as we move forward.

The experiences of the IBS community with the drug alosetron over the last 10 years provide a compelling example of the effects of risk and risk mitigation strategies on a patient community. However, this example only illustrates a broader problem faced by all functional GI and motility disorder patient communities.

The alosetron experience has taught us:

- That risk associated with a drug can be managed
- That impact of adverse events can be reduced or eliminated
- That patients may be well informed about potential benefits of drugs, but ill-informed about potential risks of drugs
- That how risk is communicated may have an effect on access
- That patients and the public need to be educated about treatment-related risk so that they can, as safely as possible, take advantage of effective therapies
- That patient risk acceptance is interwoven with severity and the burden of the disease
- That understanding the patient perspective is a critical part of an effective Risk Management Program

What is IBS?

IBS affects 10–15% of the general population, and results in high health care utilization.[5] It is characterized by a cluster of symptoms that are chronic, variable, and unpredictable.[6] Pain or discomfort is the key symptom, and the pain is related to changes in bowel habit. For about one-half or more of those afflicted, it is a life altering condition, and for many the symptoms are disabling. Despite its prevalence, there are few treatments, and often they are only marginally effective.

In women with severe IBS with diarrhea (IBS-D), alosetron may provide global improvement in IBS symptoms; adequate relief of IBS pain and discomfort, and improvement in bowel symptoms.[7–12]

What is alosetron?

Alosetron hydrochloride is a selective and potent 5-HT3 receptor antagonist; it blocks serotonin signals that transmit sensory information (painful and non-painful) from the gut to the brain and helps to reduce diarrhea and abdominal pain.[4] The drug is prescribed for the treatment of women diagnosed with severe irritable bowel syndrome (affected for 6 months or longer):

- where diarrhea is the predominant bowel symptom, and
- who have had an inadequate response to another therapy.

Under the RMP, the diagnosis of IBS is considered *severe* when the patient experiences *1 of the following 3* criteria:

- Lots of painful abdominal cramps or bloating,
- Loss of bowel control, or
- Restriction in daily activities because of the need to be near a bathroom.

Alosetron was initially approved in the United States in February 2000 for women with IBS with diarrhea, and was voluntarily withdrawn by the sponsor in November 2000 due to infrequent reports of ischemic colitis (N=83) and complications of constipation (N=98), and rare outcomes of transfusion, surgery, and death.[3] The drug was reintroduced in the U.S. market in 2002.

Ischemic colitis was reported to occur early in the course of alosetron treatment in the majority of cases, with 65–74% of cases occurring within the first month.[4]

Constipation was reported in about a quarter (18–24%) of the patients with ischemic colitis. Approximately half (40–50%) of patients were managed as outpatients, and no dose response relationship was established.

The precise pathophysiologic causes and specific risk factors of ischemic colitis associated with alosetron or other 5-HT3 receptor antagonist use remains unknown.

Constipation, however, is a recognized dose dependent, pharmacologic and class effect of 5-HT3 receptor antagonists, including alosetron.[4] Constipation was the most common adverse event reported in alosetron trials.

Serious complications of constipation (defined by the FDA and the sponsor as impaction, ileus, obstruction, perforation, intestinal ulceration, or toxic megacolon) were reported in alosetron clinical trials and in spontaneous post marketing reports before withdrawal. Unlike constipation, a dose-response relationship has not been established for the complications of constipation.[4]

Risk management program

Alosetron was reintroduced to the U.S. market in November 2002 under a Risk Management Program (RMP). Under the program, to reduce the risk of adverse events, the drug is prescribed:

- to women with severe IBS-D, and
- at a lower starting dose than originally approved.

The RMP includes a prescribing program that enrolls physicians who meet the qualifications for diagnosing and managing IBS and drug adverse events (ischemic colitis and severe complications of constipation), and who agree to specific responsibilities.[13] The program requires enhanced patient monitoring – especially during the first month of therapy – and educational components for physicians and patients for early recognition and appropriate management of constipation, ischemic colitis, and complications of constipation.[4,14]

The RMP and physician prescribing program includes

- Women with severe IBS-D
- Lower starting dose
- Qualified physicians
- Enhanced patient monitoring

Resulting in

- Patient and physician education
- Prompt recognition of events
- Management of adverse events

Recent studies that have evaluated the incidence rates of ischemic colitis and complications of constipation since the reintroduction of alosetron under the Risk Management Program suggest that the incidence of these events has remained rare and stable. Cases are typically of short duration, which resolve upon withdrawal of alosetron treatment. There were no surgeries or deaths in the patients with the possible or probable ischemic colitis and constipation complications.[4,9,14]

It is further suggested that physician and patient education as designed by the Risk Management Program has increased awareness. This has resulted in prompt recognition and treatment of adverse events, and contributed to improving outcomes of the events associated with the use of alosetron.

An evaluation by Chang and colleagues published in 2010 points out the effectiveness of the Risk Management Program. Under this plan, patients may safely take the drug.[4] Clearly risk is being managed. But what about benefit?

The effect of access on benefit

There was a large public outcry from patients when alosetron was withdrawn. Yet after reintroduction, relatively few patients are accessing the drug even though our findings show that patients remain dissatisfied with other available treatments.[15]

In 2002, when the Risk Management Program was established, we concluded there was a lack of understanding associated with the patient experience of illness and the burden of disease associated with IBS. This may have led to unintended consequences involving benefit and access.

Under the Risk Management Program, alosetron has been shown to be a safe and effective treatment. It is the only prescription drug available in the U.S. for the treatment of global symptoms of IBS with diarrhea. Yet, to date few patients have access to alosetron for various reasons.

Significantly, a decade later there appears to be reluctance on the part of the medical community to be part of the prescribing program. Therefore, patients may find it difficult to find a provider who will prescribe the medication.

Moreover, IFFGD has accumulated data that finds patients negatively view a drug removed from the market because of a potential but unproven risk, even after it is later brought back to market.[15,16] Thus, patients may in effect be deprived of a potentially beneficial treatment option. It raises the question: How can access be improved?

How can access be improved?

Risk management, understanding risk, and putting risk into perspective when it comes to the burden of chronic disease is complicated. There are few medications that have been developed specifically to treat IBS and currently there are only three that are FDA approved: alosetron for IBS with diarrhea, lubiprostone for IBS with constipation, and linaclotide for IBS with constipation. (As of this publication date, one other newer drug is under review for approval by FDA; rifaximin for non-constipation IBS.)

In an environment where there is little information available about medication risk behavior in IBS patients, we find these patients taking a variety of other medications. Significantly, none are universally effective, and all have side effects or associated adverse events.

The patient experience

In an effort to understand how patients view risk and the burden of disease in IBS, IFFGD and others have surveyed this patient population. In 2002 we surveyed 350 patient respondents from our database who reported having an IBS diagnosis to learn about their real world experiences with managing their IBS. This survey shed light on patients' experiences with health care providers and treatments.[17]

Nearly half (47%) of these respondents reported daily episodes of IBS symptoms and 71% reported two or more episodes per week. The median age was 51 years; two-thirds (64%) had been living with IBS for 5 or more years, and 42% had been living with the disorder for 10 or more years.

These patients reported using 281 different treatments including prescription drugs, over the counter medications, and herbal and dietary supplements to control their symptoms. Eighty-eight percent (88%) of this sample reported using 143 different prescription drugs, 71 OTC medications, and 67 herbal remedies, seeking to treat their IBS symptoms.

Of those taking prescription drugs, 62% reported side effects. Almost half (45%) reported the side effects as severe or moderate. Those reporting side effects also reported adverse events. One out of four had to either call (29%) or visit (24%) their health care provider. One out of five had to stop driving (22%) or reported missing work or school (18%). Twelve percent (12%) had to visit an ER, and 7% were hospitalized.

In 2007 IFFGD sponsored and collaborated with the University of North Carolina Center for Functional GI and Motility Disorders to conduct a comprehensive online survey of patients diagnosed with IBS to further understand their illness experience and unmet needs. Results were made available in 2 formats: in a peer-reviewed journal and in a publication for the general public. Among several things, we looked at how patients evaluate success of symptom relief and what risks they might assume to achieve that relief.[15,16]

Data from 1,966 qualifying responses was analyzed. Two-thirds of these respondents suffered moderate to severe symptoms. Their average age was 40 and at the time they took the survey, their symptoms had been present for an average of 15 years.

To understand patient's *expectations for symptom improvement* with a medication, respondents were asked:

> "You start taking a medication for your IBS that costs $50/month. How much better would you need to feel to continue taking this medication?"

Overall, participants report that they would need to feel at least 66% better to continue with the medication, indicating an acceptable level of improvement for any IBS medication. This finding is similar across all severity levels and IBS symptom subtypes.

Three out of 4 participants (76%) were taking medications at the time of the survey, ranging up to 13 different classes of medications, with the average respondent taking 2 drugs for IBS.

The most common medications were non-narcotic pain medications (31%), antidepressants for pain (31%), acid reducers (28%), and anti-diarrheals (24%). About 1 in 5 were taking antispasmodics (19%), and narcotic pain medications (18%).

It is noteworthy that all of the medication categories caused severe or moderate *side effects* for respondents. Those most associated with side effects were anti-constipation drugs (23.3%), narcotic pain medications (13.2%), antidepressants (13.0%), antibiotics (10.0%), and antispasmodics (9.4%).

Twenty-one percent (21%) of respondents reported ever using the IBS-targeted drugs alosetron or tegaserod, but less than 2% were taking these drugs at the time they completed the survey. Thirteen percent (13%) were taking these drugs at the time they were removed from the market by the FDA; nearly half (45%) of those found the withdrawal considerably or completely disruptive to the control of their IBS.

FDA decisions have considerable impact. Over one-half (57%) of respondents say that if a drug with a *potential but unproven risk* were removed from the market, they would feel greatly or completely affected by the decision; 38% would be greatly or completely worried to take the medication; and 56% would believe that the medication may have already caused harm.

"FDA decisions have considerable impact. If a drug with a potential but unproven risk were removed from the market, most would believe that the medication may have already caused harm."

Opinions vary about keeping the drug off the market after FDA withdrawal. About one-half (48%) would prefer that the medication stays off the market until the question of potential risk is resolved. About one in five (19%) would prefer that the medication be placed back on the market.

If the medication were to become available again, these respondents are open to abiding by several conditions: 14% would accept a warning label. About 1 in 5 (18%) would agree to sign a waiver form with the physician in addition to the warning label. One in 3 (33%) would favor prescribing only by a GI specialist as well as accepting a warning label and signing a waiver form with the physician.

When the IBS-targeted drugs, alosetron and tegaserod, were taken off the market by the FDA, 260 respondents (13%) were taking these drugs at the time of removal; 9 individuals were taking both drugs, so the total number of cases in this study is 269.

When asked, "How disruptive was medication withdrawal to your IBS *control*?" Nearly half (45%) found the withdrawal considerably or completely disruptive to the control of their IBS. When asked, "How disruptive to your *daily life* was medication withdrawal?" One-third (35%) found the withdrawal considerably or completely disruptive to their daily lives.

Acceptance of risk

Respondents were asked how much risk they would assume to take a medication providing total relief from IBS symptoms, but with serious adverse effects. Two questions were posed considering some risk of death and chance of serious permanent side effects.

Their responses are striking and suggest just how crucial symptom relief is to their well-being. Many patients are clearly willing to trade risk for relief. If offered a medication that would give them total relief of IBS symptoms: 8% of all respondents would accept a 1 in 100 chance of death; and 6% of all respondents would accept a 1 in 100 chance of serious and disabling side effects. These figures are considerably higher among the group with *severe* IBS, indicating they will accept even higher risk levels (15% would accept a 1 in 100 chance of death and 11% would accept a 1 in 100 chance of serious and disabling side effects).

A study by Johnson and colleagues published in 2010 aimed at quantifying the maximum acceptable risk (MAR) of treatment related adverse events that women with IBS with diarrhea are willing to accept in exchange for symptom relief.[18] The Web-based study included 576 women with a physician diagnosis of diarrhea predominant IBS (self reported). Adverse events were identified as impacted bowel, severe colitis, and perforated bowel. Mean age of respondents was 47 years and the mean length of time since they had been diagnosed was 10 years.

The subjects in this sample were willing to accept higher levels of risk in return for greater improvement in symptoms. Respondent choices indicated systematic preference for a treatment that provided larger reductions in symptom frequency. In this survey respondents indicated that relief of abdominal pain and discomfort (the overarching symptoms of all types of IBS) was more important than eliminating the adverse event risks.

The authors surmise that patient perspectives on balancing benefits and risks would be useful in informing both treatment and regulatory decisions. They concluded that risks often are inseparable from efficacy and that one cannot easily define what level of risk is intolerable without references to the benefits associated with increased risk.

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The benefit aspect of benefit to risk ratio is critical. Biomedical research may have to consider a wider range of treatment targets (endpoints). More research into endpoints from the patient perspective needs to be considered. Efforts like the Patient-Reported Outcomes (PRO) Consortium through the Critical Path Institute is a Private/Public Partnership that hopefully will provide a better understanding of patient needs and enhance product development and labeling.

Severity factors

Severity level is an important consideration when making treatment decisions. How is severity defined and by whom, the physician observer or the patient with the disease? What things factor into severity for any given population within a disease category? There has been little guidance offered by experts in determining when benefits outweigh risk in order to help decision-makers evaluate such trade-offs.

In 2011 the Rome Foundation, through a Working Team consensus report, published guidelines to better describe severity in IBS. Unlike many diseases where severity can be measured by abnormality in blood or tissue markers, severity in IBS and other functional GI disorders is determined by symptom reports and patient experiences.[19]

The Rome Foundation report concluded that severity is defined by a composite of patient reports:

- Symptoms in the GI tract
- Symptoms outside the GI tract
- Degree of disability
- Degree that illness relates to activities

The report further described severity as being affected by biological function and activity factors in both the GI tract and the central nervous system. As severity increases, the central nervous system provides a greater contribution. Severity is related to and influences health-related quality of life and behaviors, and also guides diagnostic and therapeutic clinical decision making. Severity in IBS can be subcategorized into clinically meaningful subgroups as mild (about 40%), moderate (about 35%), and severe (about 25%), and this provides a working model for use in future research and clinical care.

Future work is required to understand more precisely the factors contributing to severity and to develop a valid patient-reported instrument to measure severity in IBS and the functional GI/motility disorders.

The future of drug safety

The Institute of Medicine report published in 2006, *The Future of Drug Safety,* a study requested by the U.S. Food and Drug Administration (FDA) to address recognized shortcomings of the U.S. drug safety system, noted that, "In both the preapproval and the post marketing setting, the risk-benefit analysis that currently goes into regulatory decisions appears to be ad hoc, informal, and qualitative."[20]

The FDA's *Strategic Plan for Risk Communication* (SPRC) was released in 2009. In September 2010 the FDA publicized their agenda describing topics in risk communication research. The topics represent the FDA's assessment of high priority research needs for improving communication about FDA regulated products. Four key points are summarized here:

- Knowing our Audience(s): Depending on who the audience may be, determine what, when, and how the audience needs to receive risk information.
- Reaching our Audience(s): Identifying avenues to amplify FDA's messages, from partners in spreading the word, to technological channels.
- Ensuring Audience Understanding: Presenting the available information clearly, even when important facts may be unclear and/or changing.
- Evaluating Effectiveness of Communications about Regulated Products: Identifying methods to test and improve how well we communicate.

In this last bullet point the question is asked: *What levels of risk will audiences accept for different products*? This is the critical question that we all struggle with in this decision making process. It remains complicated by our definitions of severity and the burden of any disease. There have been too few studies that take into consideration the patient perspective. The studies cited above are important starting points.

Lessons from alosetron

This brings us back to alosetron. This was the first single medication available on the U.S. market demonstrated in well-designed and well-controlled clinical trials to be superior to placebo for the treatment of IBS. After it was withdrawn from the market and reintroduced in 2002, IFFGD began a continuing campaign of going to Capitol Hill, and talking to Congressional leaders about the importance of addressing 3 key issues:

1. That regulators within the FDA be made aware of the burden of illness endured by the IBS patient
2. That the FDA, as they continue to assess the safety and efficacy of medical treatments for IBS, appreciates the magnitude of pain and suffering endured by many patients
3. That the FDA applies a standard for the assessment of burden of illness in IBS that is consistent with all chronic and debilitating (non-fatal) conditions

A systematic review and meta analysis published in 2009 conducted by Ford and colleagues looked at the efficacy of 5-HT3 antagonists and the 5-HT4 agonists in IBS. They looked at alosetron and tegaserod, concluding that these drugs are effective in the treatment of IBS and should be considered for use in patients who have failed other therapies.[10]

The authors note the FDA restrictions and the need to carefully consider risk-benefit ratio when prescribing alosetron. They also point out the lack of consistency by the FDA in establishing criteria to evaluate the safety and efficacy of drugs to treat functional disorders compared with drugs to treat other conditions. The authors cite the example of the availability of NSAIDs, which are modestly effective analgesics. The use of these agents is associated with an increase risk of myocardial infarction, in addition to the well-established risk of GI bleeding, yet their use remains entirely unrestricted and in the U.S. and most countries they are freely available for purchase over-the-counter. The authors point out that use of standardized criteria may allow a more generalized use of the drugs for IBS, a disorder that is difficult to treat.

“Being told a list of possible side effects is not the same as being taught about risk.”

The functional GI and motility disorders patient population continues to ask for consistent criteria to evaluate the safety and efficacy of drugs to treat these disorders as compared with drugs that treat other conditions.

Risk-benefit is a concept that is unfamiliar to many people. Marketing emphasizes benefits; we go to doctors seeking benefits. But how many understand that medical treatment benefits don’t usually mean cure, and that many drugs are modestly beneficial, helping to feel better but not always well. Likewise, an understanding of risk, not just benefit, is crucial to patients. Being told a list of possible side effects is not the same as being taught about risk.

People go to a doctor when they need help. Their first (and most likely only) thought as patients is they need some relief. They are not thinking about the fact that the treatment they are offered may bring with it the possibility of other new problems, that there is risk associated with it. This may come as an unsettling surprise.

Consider what happened when alosetron was withdrawn from the market and then reintroduced. Prior to June 2002, the number of patients prescribed alosetron was 316,882; the total after the reintroduction from November 2002 through June 2008 was 29,072.[4]

The majority of patients who had been taking it prior to withdrawal have not returned to it. Fewer physicians are now prescribing it and fewer patients are asking for it. This is despite the finding mentioned earlier that nearly one-half (45%) of those in our 2007 survey who had been using alosetron found the withdrawal considerably or completely disruptive to the control of their IBS.[15] What is more, alosetron remains the only IBS drug on the market for treatment of global symptoms of IBS with diarrhea.

It raises the question, where have these patients all gone? As our survey showed, many have a reluctance to take a medication that is so pointedly linked to potential risk.[15,16] They have reverted back to managing in ways that they did prior to the advent of alosetron. Yet, all of these alternatives carry their own risks of adverse events. A major difference appears to be how those risks are communicated.

A recently completed sub-analysis,* reported here, of the data collected in our *International Survey of Patients with IBS*,[15] looked further at the group of respondents who had either *used* alosetron (N=87) or who were *eligible* to be prescribed alosetron based on symptom severity and disability reports matching the prescribing information (N=369).

*Funding for this sub-analysis was provided by Prometheus Laboratories, Inc.

From this study sample, the profile of the patients who had used alosetron compared to patients not on this medication showed that their illness ranked as more severe than those who had not used it, on many axes, including:

- Higher symptom severity by several measures
- Poorer health related quality of life
- More likely jobless and restricting daily activities due to health
- More likely to have incontinence
- More limited on ability to leave home

However, of the group *eligible* to use alosetron, 43% reported pain or discomfort every day and 43% self-rated their severity as *very* or *extremely* severe. Yet, only 19% had ever used alosetron.

These data suggest physicians may be using more stringent criteria than necessary to prescribe this medication. It is therefore possible that patients with less severe symptoms (while still meeting the prescribing criteria of severe) may also benefit.

"Engaging patients – not as consumers, but as partners – will help ensure more successful clinical outcomes."

There is a need for better education for the public about benefit and risk. With the understanding that all medications have inherent risks, the informed patient will best be able to weigh risk and benefit when considering a treatment, will seek to learn how to manage risk, and thus improve outcomes.

Outcomes improved with alosetron under the Risk Management Program. This is happening, not because of a drop in the incidence of adverse events, which have always been rare, but because the risk factors are recognized and events promptly managed.[3,4]

Summary

Patients managing chronic illnesses, like IBS and other functional GI and motility disorders, do best medically when they work in partnership with their physician. They need to:

- Be educated to *understand their disorder*, including its natural progression, and treatment options
- Be taught to have *reasonable expectations* about the nature of their illness, the level of benefit their treatment may achieve, and the risk associated with the treatment
- *Understand the risk tied to benefit* and the factors that affect both – like prior history, multiple medications, or lifestyle choices
- *Know their risks* including what they are and how to reduce them, how to recognize adverse events, and what to do when they occur

The FDA Safe Use Initiative, introduced in 2009, encourages public and private collaborations intended to reduce medication risks. As pointed out in their fact sheet, "All medications have inherent risks and when a person decides to use medication, he or she is agreeing to take certain risks. Some of the risks are *unavoidable*, while others can be *avoided and managed*."[21]

Regulators, manufacturers and marketers, clinicians, and patient organizations, like IFFGD, can all help individuals establish realistic expectations and goals for treatments.

Patients go about living the best they can in the everyday world that is not very scientific. It is imperfect, filled with uncertainty, as well as promise and hope. Those who suffer chronic, painful, or debilitating illness will seek relief wherever they can find it. If a well regulated drug is not accessible, not surprisingly, these patients will seek relief from something else.

Those most in need, those who suffer most, are most vulnerable in their search for relief to unregulated alternatives. They need to have access to reliable choices and they need help in making informed choices.

Effective health care outcomes involve active participation both of physicians and patients. Individuals are taught how to be doctors; we also need to teach people how to be patients.

The lessons from alosetron show us that risk can be controlled. But reducing risk of a drug, through a risk management plan, is of little use if the benefits to patients are somehow denied, for example, by lack of access.

It takes a partnership of regulators, manufacturers, physicians, and patients working together to advance mutual understanding. Regulators, industry, and physicians must do more than educate the public and support the patient. They must also *learn from patients*:

- to appreciate the severity of their illness,
- how they experience their illness, and
- how these factors affect their behavior, including the treatments they pursue and the risks they will take.

Through joint efforts, we believe the goal of safer, effective, and accessible treatments is achievable. To accomplish this, patients must be heard as well as informed. Engaging patients – not as consumers, but as partners – will help ensure more successful clinical outcomes.

Talk to your doctor about both benefit and risk. Consider:

- **How severe is your own condition – what effect is it having on your life**
- **What is the possible benefit from the drug being prescribed or suggested to you**
- **In the context of your personal illness status, what are the chances that you will receive benefit from the treatment**
- **How much benefit should you reasonably expect**
- **What possible side effects might there be from the treatment**
- **In the context of your personal health status, what are the chances that you will experience a side effect or serious adverse event from the treatment**
- **What can you do to reduce the chances of side effects**
- **How will you know when a side effect occurs**
- **Exactly what should you do if a side effect occurs**

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Published by:
International Foundation for Functional Gastrointestinal Disorders (IFFGD), Milwaukee, WI

Funding for the printing of this publication was provided by Prometheus Laboratories, Inc.

International Foundation for Functional Gastrointestinal Disorders

IFFGD is a nonprofit education and research organization. Our mission is to inform, assist, and support people affected by gastrointestinal disorders. IFFGD has been working since 1991 with patients, families, physicians, practitioners, investigators, employers, regulators and others to broaden understanding about gastrointestinal disorders and support research.

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