Irritable Bowel Syndrome

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Approximately 10% to 15% of the adult population suffers from irritable bowel syndrome (IBS), although in many, the symptoms are relatively mild. However, because the condition is so common, even if only one patient in 10 consults a physician, this represents a burden on health services in excess of that posed by inflammatory bowel disease. Furthermore, although there are effective treatments for inflammatory bowel disease, such as mesalazine, steroids, azathioprine, and biological therapies, there have been no new pharmacological agents available in Europe for the treatment of IBS for more than 20 years, and there are relatively few in the pipeline.[1] Despite the enormous size of the IBS problem, pharmaceutical companies have been deterred from entering this field because of the complexities of the underlying pathophysiology as well as the excessive demands of the regulators in terms of safety and the lack of agreement on suitable outcome measures. It is now recognized that IBS is a multifactorial problem; therefore, concentrating on one particular mechanism is likely to help only a subset of individuals at best. In addition, targeting one specific receptor is quite a risky strategy because of the built-in redundancy of biological systems whereby if one receptor is blocked, another may take over its function. This may explain why the more old-fashioned "dirty" drugs such as tricyclic antidepressants seem to be relatively useful in IBS. It may also account for why probiotics are of benefit in IBS as they too have such a wide range of different activities.

Our understanding of the pathophysiology of IBS has advanced considerably during the last two decades.[2] IBS was initially thought of as just a disorder of motility, but it is now recognized to be a complex interaction of physiological and psychological phenomena on which impinge a whole host of exogenous factors such as microbes and nutrients (Table). There is also a strong familial incidence of the condition,[3] suggesting that genetic factors[4] as well as social learning are important. Thus, there is compelling evidence that IBS is multifactorial in origin.

There are currently two models for explaining disease expression: the biopsychosocial and the heterogeneity models. The former attributes disease to the interaction of physical, environmental, and psychological factors,[5,6] and the latter considers the possibility that IBS is not a single entity but a collection of disorders with different etiologies. Obviously, both of these hypotheses have major implications with respect to treatment and especially the development of new therapeutic modalities.[1]

TABLE Putative Pathophysiological Mechanisms in Irritable Bowel Syndrome

Abnormal motility
Disturbed visceral sensation
Abnormal central processing of gut sensations
Inheritance
Dietary factors
Inflammation
Gut bacterial imbalance
Neuroendocrine factors
Psychological factors

With this increase in the appreciation of the diverse pathophysiology has come a greater awareness of the clinical manifestations of the disorder, such as the fact that it is just as common in the elderly[7] and that symptoms can be extremely severe, especially in patients referred to secondary care. Female patients liken the pain to that of childbirth,[8] the bloating can be accompanied by an increase in girth of up to 12 centimeters,[9] and the bowel dysfunction can be extreme. For instance, the diarrhea is not infrequently accompanied by fecal incontinence, and it has been shown recently that long-term constipation can be as much of a risk for pelvic floor damage as giving birth.[10]

Another facet of IBS is the tendency of patients to experience a variety of noncolonic symptoms such as backache, lethargy, and a range of urological as well as gynecological symptoms.[11] Of the latter, dyspareunia is common, and this may partly explain why so many women find that IBS interferes with sexual function.[12] These noncolonic symptoms are also important because they may result in general practitioners referring patients to the wrong specialty. For instance, if the back pain is prominent, it might be considered orthopedic or if the pain is worse with menstruation, which is very common in IBS, a gynecological opinion might be sought.[13,14] In this type of situation, patients can be subjected to a variety of inappropriate investigations or even undergo unnecessary surgical interventions. Not surprisingly, with all of these issues affecting their lives, individuals with IBS can experience an erosion of quality of life (QOL),

which may become so poor that it can be worse than that suffered by patients with end-stage renal disease or diabetes.[15] As a result, a sense of hopelessness can be engendered, which can lead to patients feeling suicidal,[16] especially in view of the notorious inadequacies of treatment and the prospect of no relief of their symptoms in the future.

The management of IBS is difficult as it involves a "trial and error" approach that often is time consuming and frustrating for both patient and physician alike. Dietary manipulation has to take into account the fact that sufferers may actually be intolerant of foods that are traditionally considered healthy. Consequently, cereals may have to be avoided because they contain insoluble fiber.[17] Fruits and vegetables may cause problems due to their content of fermentable oligo-, di- and monosaccharides and polyols.[18] The mainstay of pharmacological treatment is the use of antispasmodics in combination with antidiarrheals or laxatives as appropriate. If these fail, then antidepressants either of the tricyclic or serotonin reuptake inhibitor class can be tried; gastroenterologists favor the former,[19] despite trial evidence suggesting that both classes are equally effective.[20] Once all pharmacological approaches have been exhausted, a variety of behavioral techniques can be offered, including psychotherapy, hypnotherapy, and cognitive behavioral therapy.[21] In addition, it has been shown that patients with IBS are frequent users of complementary and alternative therapies[22] such as homeopathy.

With the possible exception of tricyclic antidepressants, the drugs that are currently at our disposal target only one of the putative pathophysiological mechanisms of IBS and therefore, for instance, antidiarrheals may improve loose bowels but do nothing for pain. Likewise, antispasmodics may improve pain but have little or no effect on bowel habit. Consequently, it may be necessary to use combinations of these medications, and even then it is difficult to address all the mechanisms involved in a particular individual. Thus a case could be made for the concept that developing a preparation with a variety of activities might have considerably more potential in the treatment of IBS than the current approach of concentrating on compounds with a narrow spectrum of activity. It is difficult to predict which would be the most rewarding combination of abnormalities to address, but based on the current state of knowledge, an effect on motility, visceral hypersensitivity, inflammation, and possibly the central nervous system (especially in cases of anxiety) would seem to be an obvious goal. However, another hurdle to testing such an approach is the problem of the design of clinical trials in this area.

In order to try to improve the quality of clinical trials in IBS, a variety of diagnostic criteria have been developed. The first is the Manning Criteria,[23] followed by various versions of the Rome Criteria, of which Rome III[24] is the most recent (although how this latest version compares with the previous ones remains to be determined). The Rome criteria are the most widely used, although the Manning Criteria still have a lot to commend them. Certainly the development of criteria has greatly improved the homogeneity of patients entering clinical trials, although they give no indication of severity. There are only two instruments for measuring severity: the Functional Bowel Disorder Severity Index[25] and the IBS Symptom Severity Score.[26] The latter is specific for IBS, is used widely for assessing severity, and can be used as an outcome measure in terms of defining a responder as a 50% reduction in his or her score. However, this instrument has the disadvantage that a 50% reduction of a high score may not be clinically similar to a 50% reduction of a low score, although there are some data to suggest this may not be such a problem as might be expected.[27]

Other outcomes are designed to capture improvement in terms of whether, compared with how they were before treatment, patients consider their symptoms to be adequately or satisfactorily relieved.[28] The US Food and Drug Administration (FDA) has recently announced that it considers all the currently used outcome measures in IBS suboptimal. The FDA has therefore initiated a program of development of a patient reported outcome measure, although the final version will not be available for a few years. In the meantime, trials will continue to use existing outcome measures. All clinical trials in IBS should also be accompanied by a QOL assessment. A number of these are available, but the IBS QOL is probably the most widely utilized.[29]

The final obstacle to drug development in this field is the very strict line on safety that has been adopted by the regulatory authorities in relation to any new drugs for IBS.[30] This stance is based on the assumption that IBS is not a fatal condition, despite the fact that some sufferers are driven to suicide and their QOL can be poor. Regulators also fail to appreciate how desperate patients are to have some new therapeutic options for this condition. This desperation has recently been highlighted by a study showing that patients would be prepared to trade some life expectancy or risk of severe side effects from a drug in order to gain some relief from their symptoms.[31] At least these restrictions would not apply to bioregulatory medicines with their ultra low–dose formulations and resulting safety profile.

Thus in summary, there is a huge unmet need for new therapeutic options in IBS, but there are a number of impediments to progress in this area. These include knowing what mechanisms to target as well as trying to meet what could be considered to be the excessive needs of the regulators in terms of design of trials and especially safety.

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