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Many generations of medical students have received little or no tuition on the subject of irritable bowel syndrome (IBS) and when they have, they are often taught that it is not a particularly serious condition that is largely caused by psychological factors. Furthermore, the commonly held view that it is a diagnosis by exclusion only serves to reinforce the notion that there is actually nothing wrong with the individual. It is against this background that sufferers encounter the medical profession and it is therefore not surprising that, when their symptoms are severe, they feel they are not being taken very seriously.

In the majority of individuals with IBS the condition is relatively mild and they seldom, if ever, consult their doctor. However, in a relatively small proportion the symptomatology can be much more intrusive and these are the patients that are often referred to secondary and sometimes tertiary care. It is now clear that the pain, bowel dysfunction and bloating in these individuals can be refractory to the current medications and be extremely severe. For instance, many women equate the level of pain to that of childbirth [Agrawal and Whorwell 2006], and with respect to bloating, an increase in abdominal girth of up to 12 cm during the course of the day is not unusual [Houghton and Whorwell 2005]. In addition, these patients experience a variety of extraintestinal features such as backache, thigh pain, constant lethargy, urinary and gynaecological problems [Whorwell *et al.* 1986] with the latter significantly interfering with sexual function [Guthrie *et al.* 1987]. It therefore follows that quality of life is impaired and it has been shown to be worse than that experienced with more 'legitimate' medical conditions such as diabetes or chronic renal failure [Gralnek *et al.* 2000]. All these issues coupled with the prospect of no 'cure' engender a sense of hopelessness in these more seriously affected patients and it has been shown that a significant proportion become suicidal [Miller *et al.* 2004]. The resulting economic burden that these individuals place on society is substantial in terms of time off work as well as healthcare costs and this has been confirmed in a number of studies [Longstreth 1995].

In the European setting, there has been no new medication introduced for the treatment of IBS for over 20 years. In addition, those that are available are of limited value and usually only offer help with an individual symptom such as pain or bowel habit. Any potential new medication would ideally alleviate more than just one symptom and hopefully improve overall well-being and functioning. Until recently, the development of new drugs has been hampered by the lack of understanding of the pathophysiology of the condition coupled with the erroneous assumption that psychological factors are paramount. However, there is now clear evidence that a variety of factors ranging from disordered motility and visceral sensation through to abnormal central processing of noxious stimuli from the gut are involved in disease expression [Drossman *et al.* 2002]. A further development

was the discovery that a number of neurotransmitters contribute to the control of gastrointestinal function with particular focus on the modulation of serotonin receptors [Gershon, 2002]. Data from clinical trials indicated that antagonism of the $5HT_3$ receptor in diarrhoea predominant IBS [Camilleri *et al.* 2000] and agonism of the $5HT_4$ receptor in constipation predominant patients [Muller-Lissner *et al.* 2001] relieved many of the symptoms of IBS as well as leading to an improvement in quality of life. Unfortunately, both these approaches were associated with side effects leading to a robust response from the regulatory authorities despite the fact, especially in the case of $5HT_3$ receptor antagonism, patients were saying that treatment had changed their lives.

The insensitive attitude of the regulatory authorities seems to be centred on the concept that IBS 'never kills anybody'. As a consequence, they appear to be making demands relating to new IBS drugs that would not even be contemplated in other therapeutic areas with respect to the required level of therapeutic advantage over the placebo as well as demanding absolute safety. This latter requirement is senseless, as by their very nature, all drugs will have some adverse effects although obviously their acceptability has to be in proportion to the severity of the condition for which they are being developed. However, if some patients with IBS are finding their symptoms so intolerable that they become suicidal, it could be argued that they should be the judge of how much in the way of adverse effects they are prepared to tolerate. This issue has recently been addressed by Drossman *et al.* [2009] where they found that patients would be prepared to give up 25% of their remaining life in order to have a treatment that made them symptom free. Furthermore, 14% of patients surveyed would be prepared to risk a treatment that carried a 1/1000 chance of death. It seems regrettable that patients have no say in decisions that are being made on their behalf, by panels that possibly may not be familiar with the real suffering of these patients.

It has been estimated that 20–30% of IBS sufferers are referred for specialist care and those who could be classified as severe are approximately equal in number to the total number of patients with inflammatory bowel disease in a given population. Interestingly, a recent study showed that the levels of suffering of severe IBS patients exceeds that of inflammatory bowel disease, with the lack of effective medications being highlighted as one of the main reasons for this difference [Miller *et al.* 2004]. This again serves to emphasise the point that there is a substantial unmet need for new therapies for those whose lives are blighted by IBS. In addition, if new and effective drugs for IBS were made available to the medical profession it is also likely that they would manage these individuals far more sympathetically, for nothing is more frustrating than to make a diagnosis but not be able to offer any real help.

To date, potential new medications for IBS have been tested in large groups of patients selected on the basis of varied clinical criteria and in whom the pathophysiology is probably heterogeneous. In such populations, the efficacy of these drugs is bound to be relatively low and unfortunately the regulatory authorities have to base their decisions on the results of such trials. However, it is likely that the efficacy of these drugs will be much higher in more homogeneous groups of patients, but this will only become apparent after they have become available for use in clinical practice. Once that has happened, better advice on prescribing patterns can then be developed. Another obstacle to progress is that there is still no consensus on the optimal design of clinical trials in IBS particularly in relation to what is the most appropriate outcome measure.

The introduction of new drugs for IBS would inevitably lead to some increase in drug bills because the currently available medications are so cheap, although relatively ineffective. However, these consequences could well be offset to some extent by improved work performance and reduced healthcare costs in terms of repetitive referral and investigation. If the pharmaceutical companies continue to be thwarted by ill-conceived obstacles to their attempts to introduce new drugs for IBS, they are likely to abandon this therapeutic area or not venture into it in the first place. This may protect drug bills, but it will be at the expense of continued patient suffering and denial of their human rights to have help with their condition.

Conflict of interest statement

Professor Whorwell has served as a speaker, a consultant and an advisory board member as well as receiving research funding from the

following pharmaceutical companies: Novartis Pharmaceuticals, Glaxo SmithKline, Solvay Pharmaceuticals, Rotta Research, Proctor and Gamble, Danone Research, Astella Pharma, Ironwood Pharmaceuticals, Sucampo Pharmaceuticals and Tillots Pharma. Professor Azpiroz has served as an advisor and received research funding from a similar range of pharmaceutical companies.

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