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Alosetron for irritable bowel syndrome

Some patients may pay a high price for the FDA's decision to put the drug back on the market

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On 9 February 2000 alosetron (marketed as Lotronex by GlaxoSmithKline), a type 3 serotonin (5-HT_3) receptor antagonist, was approved by the US Food and Drug Administration (FDA) for the treatment of patients with irritable bowel syndrome, a benign though unpleasant disorder that affects one in five adults in the industrialised world.[1] By November 2000, the FDA had received 49 reports of ischaemic colitis and 21 of severe constipation related to the drug, resulting in 44 admissions to hospital, 10 surgical interventions, and 3 deaths.[2] The drug was withdrawn from the market by its sponsor. Severe adverse events continued to be reported for some time, with a final total of 84 instances of ischaemic colitis, 113 of severe constipation, 143 admissions to hospital, and 7 deaths.[3]

On 7 June 2002, however, the FDA issued a supplemental new drug application that permits marketing of alosetron through a prescribing programme for treating women with irritable bowel syndrome whose main symptom is severe diarrhoea (5% of patients). Doctors will have to sign an attestation of qualification and acceptance of responsibilities. Patients will have to sign a patient-physician agreement attesting that they have been adequately informed of the risks and that they have the form of irritable bowel syndrome that may be treated with alosetron.[4]

This prescription programme is unlikely to prevent severe adverse reactions due to alosetron. In November 2000, the FDA's office of post-marketing drug risk assessment underlined that ischaemic colitis could not be predicted, some patients were not able to recognise the signs and symptoms of constipation, the reversibility of ischaemic colitis had not been established, and the signs and symptoms of these severe adverse effects were too similar to those of the disease being treated.[2] The increasing number of severe adverse experiences reported after the "Dear Doctor" and "Dear Pharmacist" letters issued in June 2000 at the request of the FDA also suggests that a real and effective risk management policy is not possible. The FDA's decision to put alosetron back on the market was made despite strong opposition of an insider (read Paul Stolley's story, p 592), and dissent is now being voiced by members of the advisory committee (see p 561).

According to the information given in the patient-physician agreement, severe constipation occurred in about 1 in 1000 patients treated for six months, and ischaemic colitis in 1 in 350. The present prescription plan would theoretically allow up to two million people in the United States to receive alosetron, which might result in 2000 cases of severe constipation, 5714 cases of ischaemic colitis, 1109 surgical interventions, and 329 deaths; 240 000 women would experience some relief of symptoms.[5] The price to pay for this benefit looks very high.

What can have driven the FDA to reinstate alosetron on the market, while stating in the same letter that the drug "poses a serious and significant public health concern?" Lobbying by the Lotronex Action Group may be one reason. This group has been formed on the initiative of people belonging to the IBS Self Help Group.[6] The IBS Self Help Group does accept sponsorship from companies, and GlaxoSmithKline's banner is displayed on its website.[7] The group claimed that alosetron conferred life changing benefits on a large number of users on the grounds of a survey conducted by Drug Voice, a profit making "consumer research and marketing company specialising in taking the consumer's voice to pharmaceutical and healthcare leaders."[8]

A second reason for reinstating alosetron may be lobbying from the pharmaceutical industry. With 40 million potential patients in the United States, irritable bowel syndrome is a gold mine of the size of hypertension or type 2 diabetes. GlaxoSmithKline is obviously not the only one to crave this new market: the IBS Self Help Group's website also displays banners of Novartis and Solvay Pharmaceuticals, two laboratories that seek to enter the United States market for irritable bowel syndrome with tegaserod (a 5-HT_4 antagonist) and cilansetron (a 5-HT_3 antagonist) respectively. With massive direct industry funding of the FDA through the Prescription Drug User Fee Act, some doubts can be expressed about the ability of the agency to resist pressure from industrials.[9]

A third reason may be a shift in the FDA—from being traditional and paternalistic to holding a more republican view of public health. The agency would now rather provide the best information for patients and doctors to make their own decisions than to make the decisions in their name.

The main mission of the FDA's Center for Drug Evaluation and Research is to "protect the public health by ensuring that human drugs are safe and effective."[10] By allowing the marketing of alosetron, a drug that poses a serious and significant public health

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concern according to its own terms, the FDA failed in its mission. Moreover, in waiving its responsibility, the agency transferred it to the patients, asking them to attest that they belong to the target population and can manage the risks. Most patients obviously lack the background and training necessary to assess correctly the balance between risk and benefit, and they may be misled by self help groups that have financial ties with the pharmaceutical industry. If the decision regarding alosetron is the harbinger of future FDA policy, the entire population of the United States will need full medical training, with access to genuinely independent therapeutic information.

Michel Lièvre *associate professor*

Clinical Pharmacology Unit, Faculté de Médecine Laënnec, BP 8071, 69376 Lyons Cedex 08, France (ml@upcl.univ-lyon1.fr)

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When medical students go off the rails

Student support is essential, but so is protecting the public

Medical students can acquire the knowledge and skills that they need only by coming into close contact with vulnerable members of society. Once they graduate, new doctors are expected to conform to principles of professional conduct that have the safety of patients at their heart,[1] so the award of a medical degree confirms more than academic achievement. It says that the graduate is fit to practise under supervision as a doctor and can be trusted by public and profession alike. In the United Kingdom, graduation in medicine automatically leads to provisional registration as a doctor, and the regulatory body has no discretion in the matter.[2]

Medical schools therefore have a considerable responsibility to identify and appropriately manage students whose conduct may put patient safety at risk. No member of the public should be harmed by participating in the learning of students or through the actions of a newly graduated doctor who is not fit to practise.

Examples of conduct that would seriously call into question the suitability of medical students to continue with their course and enter practice include exploiting vulnerable patients, dishonesty, repeated inappropriate behaviour, or failure of treatment for chronic substance misuse.

This is a little researched area, and systematic analyses are not available. Internationally several approaches to the management of student misconduct exist. In New South Wales, for example, the doctors' licensing authority also registers medical students from the start of their course, enabling continuity of supervision, with the added advantage of separating responsibilities for academic and conduct or health issues.[3] There are, however, potential legal obstacles to this approach in some jurisdictions. Strict privacy laws that are included in much legislation about human rights may limit the information that can be passed between organisations, at least without consent. Also the prospect of a third party terminating a student's course could prove challenging. Elsewhere many universities rely on regulations and honour codes, with medical students being regarded in the same way as other students.[4] Most medical schools in the United Kingdom have taken a different approach with the introduction of procedures that specifically consider fitness to practise separately from academic matters.[5]

Whatever process is used for managing misconduct, the first step is to identify it. This may not be easy, except in cases of grossly dysfunctional behaviour, and a pattern is often built up over time. Medical schools should have mechanisms in their assessment and appraisal systems to identify students whose conduct is causing concern. Effective reporting and central recording of information is essential so that an overview of a student's progress can be maintained.

Doctors have a key role in identifying conduct problems in their colleagues. Medical schools should prepare their students for this important aspect of professional life by developing themes of learning that introduce students to their responsibility if they believe that a colleague's conduct could put patients at risk.

When an alleged problem about conduct becomes known, the medical school should have two concerns: pastoral care for the student and protection of the public. Each is important, but the latter must always take priority. If there is a prima facie case that raises serious concerns about patient safety, the student should be suspended until the matter is resolved.

Rehabilitation and return to the medical course should always be considered, but may not be possible or successful. Once a student has been dismissed from the medical school their career usually cannot be tracked efficiently. There is always the possibility that they will attempt to achieve a medical qualification—for example, in another country.

Students whose health could affect patient safety also pose special challenges. It is important to establish an environment—especially in areas such as substance misuse and mental illness—where medical students feel

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