35 years. On 1 September 2005 the government's response to the committee's report showed serious reflection on these issues.[10] The government has accepted many of the committee's recommendations, but too often its response has not gone far enough.

The committee recommended that the Department of Trade and Industry should take responsibility for representing the interests of the pharmaceutical industry, enabling the Department of Health to concentrate solely on the regulation of medicines and the protection and promotion of health. The government rejected this recommendation on the grounds that "the interests of patients and the industry are not exclusive" and that the industry's role in producing innovative medicines beneficial to health should be considered together with its economic investment in the United Kingdom. In this political context there is a considerable risk that public health will not be given sufficient priority whenever the commercial interests of pharmaceutical companies diverge from, or conflict with, health needs.

Since 1996 fewer than half of the drug innovations (new molecular entities) in the United States have offered real therapeutic advances.[9] Many are "me too" drugs: minor molecular modifications of existing products. They satisfy the technical definition of innovation and seek a slice of a lucrative market, but contribute little or no therapeutic advance for patients. The House of Commons Health Select Committee recommended that the UK Medicines and Healthcare Products Regulatory Agency (MHRA) should be more proactive in stimulating the industry to develop drugs of real therapeutic value and "therapeutic gain." Despite recognising that the existence of a large number of "me too" drugs creates difficulties for prescribers, the government remains unwilling to direct the development of drugs towards more meaningful new treatments.

The committee also felt that the deluge of promotional material doctors receive from pharmaceutical companies is excessive and insufficiently counterbalanced by independent information, especially when the manufacturer seeks to establish a market position for a newly launched drug and patients are most at risk because little is known about the product. The government, on the other hand, believes that the industry's current self regulation of drug promotion is acceptable. Nevertheless, the MHRA may extend its vetting of promotional materials to all new molecular entities and may impose additional restrictions when new drugs are first released on to the market.

The government now seems to embrace the idea of patients reporting their own adverse drug reactions using the Yellow Card scheme that is already used by prescribers. However, the government ignored the committee's call for the Department of Health and the MHRA to investigate the extent, cost, and implications of drug induced illness in our communities and to pave the way for rational cost-benefit assessment of medicines.

Issues of secrecy, transparency, and public accountability in the drug regulatory system pervaded almost every aspect of the inquiry. The government agrees that the regulatory system should be as transparent as possible. It has promised to provide public access to information on licensing applications for individual drugs, to the data supporting authorisation for marketing, and to assessments of medicines on which regulatory action is taken. This is a considerable and welcome shift in thinking and policy, but these commitments must also be implemented in practice.

The committee recommended that the MHRA should make public the material it receives from drug companies along with its assessments as soon as they are complete. This would enable scientists and doctors to scrutinise and engage with the agency's decision making processes and would ensure that drug regulation was publicly defensible and hence more robust. The government, however, insists on reaching regulatory decisions about applications for new drug licences before allowing any public access to such information. At least, though, the government has agreed that the MHRA should be independently reviewed every four or five years.

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1 Abraham J, Lewis G. R*egulating medicines in Europe: competition, expertise and public health*. London: Routledge, 2000.
2 Hilts PJ. *Protecting America's health: the FDA, business and one hundred years of regulation*. New York: Knopf, 2003.
3 Charles River Associates. Innovation in the pharmaceutical sector: a study undertaken for the European Commission. 2004. http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/nov/EU%20Pharma%20Innovation_25-11-04.pdf (accessed 4 Sep 2005).
4 Woodcock J. FDA's critical path initiative. 2 Jun 2004. www.fda.gov/oc/initiatives/criticalpath/woodcock0602/woodcock0602.html (accessed 5 Sep 2005).
5 CMR International. Latest news: innovation on the wane? 2005. www.cmr.org (accessed 5 Sep 2005).
6 Abraham J, Davis C. A comparative analysis of drug safety withdrawals in the UK and the US (1971-1992): implications for current regulatory thinking and policy. *Soc Sci Med* 2005;61:881-92.
7 Topol EJ. Failing the public health – rofecoxib, Merck and the FDA. *New Engl J Med* 2004;351:1707-9.
8 Department of Health. Press release 2003/0214, 23 May 2003.
9 House of Commons Health Committee. *The influence of the pharmaceutical industry*. 22 Mar 2005. www.parliament.the-stationery-office.co.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf (accessed 5 Sep 2005).
10 Government response to the Health Committee's report on the influence of the pharmaceutical industry, 1 September 2005. (Cm 6655.) www.dh.gov.uk/assetRoot/04/11/86/08/04118608.pdf (accessed 5 Sep 2005).

SSRIs and gastrointestinal bleeding

Gastroprotection may be justified in some patients

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There are theoretical reasons for believing that selective serotonin reuptake inhibitors (SSRIs), widely used to treat depression, might increase the risk of gastrointestinal bleeding. Gastroprotective drugs are advocated for high risk patients taking non-steroidal anti-inflammatory drugs, another class of drug that causes gastrointestinal bleeding. What is the evidence that this advice should be extended to patients receiving SSRIs?

Serotonin is released from platelets in response to vascular injury and promotes vasoconstriction and a change in the shape of the platelets that leads to

aggregation.[1] Platelets cannot themselves synthesise serotonin. SSRIs inhibit the serotonin transporter, which is responsible for the uptake of serotonin into platelets. It could thus be predicted that SSRIs would deplete platelet serotonin, leading to a reduced ability to form clots and a subsequent increase in the risk of bleeding.

We have reviewed the published database studies on the relation between SSRI use and gastrointestinal bleeding. Four of these studies compared the risk of an upper gastrointestinal bleed in those prescribed SSRIs with those who were not. The odds ratios of a bleed in an SSRI-treated patient ranged from 1.38 to 3.6: 3.0 (95% confidence interval 2.1 to 4.4),[2] 3.6 (2.7 to 4.7),[3] 2.1 (0.6 to 8.3),[4] and 1.38 (0.82 to 2.34).[5] This roughly threefold increase in risk may also hold for other types of bleeding. Movig et al reported that patients taking SSRIs were 3.71 (1.35 to 10.18) times more likely to require a blood transfusion during orthopaedic surgery than patients not taking them.[6] Meijer el al reported that women taking SSRIs with a high affinity for the serotonin transporter were 3.0 (0.8 to 4.9) times more likely to experience abnormal uterine bleeding than women who took antidepressants with low affinity for this transporter.[4]

An association between the risk of bleeding and increasing affinity for the serotonin transporter has been noted in several studies,[2 4 7] although the confidence intervals around the quoted odds ratios overlap considerably. Clomipramine, fluoxetine, sertraline, and paroxetine have a high affinity for the serotonin transporter while citalopram, fluvoxamine, and venlafaxine have intermediate affinity. Low affinity drugs include doxepin, mirtazepine, moclobemide, and nortriptyline.

Risk decreases to the same level as controls in past users of SSRIs, indicating that bleeding is likely to be associated with the drug rather than the illness it was prescribed for.[3] The association also holds when age, gender, and the effects of other drugs such as aspirin and non-steroidal anti-inflammatory drugs are controlled for.

The mechanisms by which non-steroidal anti-inflammatory drugs and SSRIs are associated with gastrointestinal bleeding are different. Non-steroidal anti-inflammatory drugs directly damage the gastrointestinal mucosa, while SSRIs reduce the effectiveness of the normal clotting mechanism. Aspirin does both. The absolute additional risk of an upper gastrointestinal bleed (requiring admission to hospital) with an SSRI prescribed alone is about 1 in 300 patient years, but co-prescription of SSRIs with aspirin increases the risk to 1 in 200 and with non-steroidal anti-inflammatory drugs to 1 in 80.[3] The risk with a non-steroidal drug alone is 1 in 200.[8]

The well established association between non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding is estimated to result in 700-2000 deaths/year in the UK.[8 9] This has led to the recommendation that patients in high risk groups should receive gastroprotection in the form of an H_2 antagonist, proton pump inhibitor, or misoprostil.[10] High risk groups are defined as patients older than 65 years, those with a history of peptic ulcer or gastrointestinal bleed, those who are debilitated, and those receiving other drugs that are associated with an increased risk of bleeding such as warfarin and corticosteroids. Yet only misoprostol has been proved to reduce the risk of serious bleeds. Proton pump inhibitors have been shown to reduce endoscopically diagnosed mucosal damage and heal ulcers induced by non-steroidal anti-inflammatory drugs but not to reduce the incidence of severe gastrointestinal bleeds.[10]

SSRIs are widely prescribed in the general population and for elderly people. Almost 14 million prescriptions were dispensed in community pharmacies in England in 2003.[11] They are recommended by the National Institute for Health and Clinical Excellence as first line treatments in patients with at least moderate depression.[12]

Gastroprotection is unlikely to be justified in patients who receive SSRIs alone, but those who are also taking non-steroidal anti-inflammatory drugs or aspirin are clearly at increased risk. This increased risk may also apply to those who are very old or have a history of gastrointestinal bleeding. The use of antidepressants with low affinity for the serotonin transporter should be considered in these patients. Gastroprotective agents have not been shown to reduce the risk of bleeds associated with SSRIs alone or in combination with non-steroidal drugs, but until such studies are conducted we recommend that SSRIs are added to the list of drugs that increase the risk of bleeding induced by non-steroidal anti-inflammatory drugs and suggest that gastroprotection should be considered in patients who are prescribed both SSRIs and non-steroidal anti-inflammatory drugs or aspirin, including those under the age of 65.

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1 Skop BP, Brown TM. Potential vascular and bleeding complications of treatment with selective serotonin reuptake inhibitors. *Psychosomatics* 1996; 37:12-6.
2 De Abajo FJ, Rodriguez AG, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding. *BMJ* 1999;319:1106-9.
3 Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding; a population based cohort study. *Arch Intern Med* 2003;163:59-64.
4 Meijer WEE, Heerdink ER, Nolen WA, Herings RMC, Leufkens HGM, Egberts ACG. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. *Arch Intern Med* 2004; 164:2367-70.
5 Layton D, Clark DW, Pearce GL, Shakir SAW. Is there an association between selective serotonin reuptake inhibitors and risk of abnormal bleeding? Results from a cohort study based on prescription event monitoring in England. *Eur J Clin Pharmacol* 2001;57:167-76.
6 Movig KLL, Janssen MWHE, Malefijt JdW, Kabel PJ, Leufkens HGM, Egberts ACG. Relationship of serotonergic antidepressants and need for blood transfusion in orthopaedic surgical patients. *Arch Intern Med* 2003;163:2354-8.
7 Van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastroinstestinal bleeding in elderly patients: retrospective cohort study. *BMJ* 2001;323:1-6.
8 Tramer MR, Moore RA, Reynolds DJM, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. *Pain* 2000;85:169-82.
9 Taking stock of coxibs. *Drug Ther Bull* 2005;43;1-6.
10 Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, et al. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database of Systematic Reviews* 2002; Issue 4. CD002296.
11 Department of Health. *Prescribing analysis and cost data.* www.publications.doh.uk/stats/pca2003.htm 2005 [accessed 10 Jan 2005].
12 National Institute for Clinical Effectiveness. *Treatment guideline for depression.* London: NICE, 2004. www.nice.org.uk