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Selective serotonin reuptake inhibitors

Remain useful drugs which need careful monitoring

See News p 816 and *Personal view* p 865

The increasing use of antidepressants—particularly the selective serotonin reuptake inhibitors (SSRIs)—might be grounds for optimism because it might indicate that one of the great health problems of our age is increasingly being recognised and treated. Instead SSRIs have become embroiled in controversy over both their effectiveness and safety. As well as the doubts about efficacy, the media have fuelled concern that SSRIs may cause serious adverse effects, ranging from worsening depression to suicide. The scientific evidence shows that the media has blown the risk of suicide out of proportion.

The increase in prescribing of SSRIs has coincided with a fall in the suicide rate in many countries, implying that SSRIs are not a major cause of suicide.[1] Case-control studies—which cannot completely rule out confounding by indication—probably exclude a substantial increase in both relative and absolute risk of suicide.[2] A meta-analysis of individual patient data from the randomised trials is clearly necessary but has not been done. Short term randomised trials of SSRIs in children and adolescents show a modest increase in some suicidal thoughts and behaviours, but it is unwarranted to assume that this translates into an increase in the risk of suicide itself, rather than reflecting the transient increase in agitation that is a recognised adverse effect of SSRIs.[3]

Despite the incomplete evidence, the concern over potential adverse effects has led to regulatory authorities issuing warnings about specific groups of patients when evidence for benefit is lacking. In the US the Food and Drug Administration has asked for a statement to be included in the relabelling of several antidepressants recommending that adults and children taking these drugs should be closely observed for worsening depression and the emergence of suicidal thoughts.[4] In the UK the Medicines and Healthcare Products Regulatory Agency has recently advised that SSRIs other than fluoxetine should not be used in children and that the dose of paroxetine should be limited to 20 mg in adults (www.mhra.gov.uk). The forthcoming National Institute for Clinical Excellence (NICE) guidelines on managing depression have been delayed until the Committee on Safety of Medicines has reconsidered the evidence on the efficacy and safety of SSRIs (www.nice.org.uk/page.aspx?o=20093). The current draft of the NICE guidelines finds that the strongest evidence for efficacy is in major depression of at least moderate severity but states that efficacy for patients with mild depression, which presents frequently in primary care, is unproved. The draft guideline indicates that SSRIs are being overused in mildly depressed patients for whom the ratio between risk and benefits is unclear but may not be favourable.

A problem that is often overlooked is that the available randomised evidence does not provide reliable estimates of the costs and benefits of SSRI treatment in patients with varying levels of severity and baseline risk of suicide. For example, placebo controlled trials seem to show that SSRIs are only slightly better than placebo.[5] Most trials are sponsored by the drug industry, which, if anything, might inflate estimates of efficacy.[6] Publication bias favouring positive trials is widespread in SSRI versus placebo trials: many of the pivotal phase three trials investigating the efficacy of antidepressants have not been published.[3 5] The potential for publication bias to cause serious bias and potential harm for many thousands of patients is well accepted, and it has been argued that legislation is now required.[7] One obvious conclusion is that SSRIs do not work much better than placebo.

There are good reasons, however, to think that these trials do not tell the whole story and that the estimates of treatment effect that they produce may be seriously misleading. Head to head comparisons with the older tricyclic antidepressants indicate that, overall, SSRIs are of comparable efficacy[8] and strategies to improve concordance with antidepressants usually lead to better outcomes.[9]

Regulators consider short term placebo controlled trials to be essential to demonstrate the efficacy of new antidepressants because of the high placebo response rate observed in the disorder.[10] Yet placebo controlled trials are difficult to conduct because of the lack of clinical uncertainty about the efficacy of existing drugs for depression. Many UK ethical committees will not approve such trials, leading to a striking and unjustifiable lack of consistency between the national ethical and regulatory bodies. Because these trials are difficult to conduct, participants in placebo controlled trials tend to be highly selected. The increasing response to placebo over time indicates that this problem is getting worse,[11] with an increasing tendency for randomised trials to be carried out on people with relatively mild disorders with high spontaneous remission rates. This situation illustrates the dangers of relying entirely on trials conducted by industry to meet the limited needs of regulators in an important disease such as depression. Most registration trials are simply not designed to answer important clinical questions and to

BMJ 2004;329:809–10

provide reliable and precise estimates of the benefits and risks of treatments. Independent trials are needed but, at least in the United Kingdom, non-commercial funding for trials is declining.[12]

Uncertainty therefore remains about the balance between benefits and harms of SSRIs. To us, however, it seems clear that the recent negative publicity about antidepressant drugs has fed into the routine stigmatisation and trivialisation of mental disorders. Doctors must not become reluctant to use antidepressant drugs in patients with clearly defined depressive disorders, but they should also monitor patients carefully in the first weeks of treatment.

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Competing interests: JG is currently in discussion with several companies that manufacture SSRIs about support for independent trials that he is planning and doing.

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Why the GMC is right to appeal over life prolonging treatment

Unless a high court judgment is overturned it will skew medical care

See News p 818

The General Medical Council, Britain's regulatory body for doctors, is surely right to have appealed against a high court ruling that its current guidance on withholding and withdrawing life prolonging treatment is unlawful.[1 2] If not overturned the judgment is likely severely to tilt the balance of medical practice towards non-beneficial and wasteful provision of life prolonging treatment in general and of artificial nutrition and hydration in particular.

The specific case on which the high court made this ruling is uncontroversial. If the existing GMC guidance were followed Mr Burke, who took the case to the high court and who has degenerative spinocerebellar ataxia, would have been treated with artificial nutrition and hydration for rather longer than Mr Justice Munby has now ruled that he *must* be treated. But the judgment itself extends far beyond the particular case and can be predicted to lead doctors routinely to provide artificial nutrition and hydration—and arguably other life prolonging treatments—for all legally incompetent patients unless either they have previously competently rejected it by a valid advance directive or its provision would be regarded by all involved as "intolerable."

In the absence of a court decision to the contrary, all babies and children, all patients dying of cancer, all brain damaged patients, all patients in intensive care, and all patients with dementia, if they are not competent to make decisions for themselves and have not competently rejected it in advance, will in principle have to be given life sustaining and prolonging treatments if their relatives or friends say it is in their best interests and do not agree that it would be "intolerable" to provide it .

Mr Justice Munby does not himself make these sweeping assertions and formally judged only the case of this particular competent patient, but their truth follows inexorably from his extensive adjudication. Essentially he argues—controversially—that combinations of articles 2, 3, and 8 of the Human Rights Act (the right to life, the prohibition of inhuman and degrading treatment, and the right to respect for private and family life), supported by other existing English law, require the following conclusions.

Firstly, patients who believe that they would "be exposed to acute mental and physical suffering" if they were denied a life prolonging treatment, and in particular artificial nutrition and hydration, would have a right to require that they be provided with that treatment (213 i,l,m,n,o and 214b,c,d,e in the judgment). Secondly, incompetent patients should be presumed to desire such life prolonging treatment and presumed to believe, at least in the case of artificial nutrition and hydration, and arguably in the case of all life prolonging treatments, that they would "be exposed to acute mental and physical suffering" if they were not given it (213 j,k,o and 214 d,e). Thirdly, the legal "best interests" test on which decisions for incompetent patients are properly taken, should, in the case of life and death decisions, be based on "intolerability." Thus except in "extreme" cases in which the court is entitled to say, "The life which this treatment would prolong would be so cruel as to be intolerable," life prolonging treatment

BMJ 2004;329:810–1