

teria were challenged with a new antibiotic class, there would be little chance of cross resistance. Resistance had clearly been controlled up to the 1970s by the many different chemical antibiotic classes available.

The late 1960s were also important for the introduction of organ transplantation. As these procedures became more successful, more aggressive antibacterial therapy was required to protect immunosuppressed patients against infections. This situation was exacerbated with the treatment of neutropenic patients. This massive increase in antibiotic use in hospitals did promote the acquisition of resistance in some well recognised hospital pathogens, such as methicillin resistance in staphylococci and vancomycin resistance in enterococci.

In reality, these labels are convenient markers. Methicillin resistant *S aureus* is resistant to aminoglycosides, often to fluoroquinolones, and indeed to all antibiotics except the glycopeptides, and there are reports that some strains are becoming resistant to these.³ In fact, these multiresistant variants of *S aureus* often occur as epidemic strains. What we are apparently witnessing is the clonal spread of a few resistant bacteria, and they are not simply the original hospital staphylococci that have become resistant.⁴ They often contain plasmids harbouring resistance genes, but these plasmids are carriers of resistance that often have “dumped” their resistance genes into the bacterial chromosome by transposition. Similarly, the so called vancomycin resistant enterococci are also multiresistant strains and they are often resistant to all antibiotics targeted against them. The bacteria often spread clonally, although some individual resistance genes may be imported on mobile genetic elements.⁵⁻⁷

We are also facing some resistant bacterial species that were never traditionally regarded as pathogens, such as *Acinetobacter baumannii*. This organism was sensitive to all antibiotics in the 1970s,⁸ but now some strains can sometimes resist all antibiotics.⁹ In the case of this bacterium, the propensity to carry resistance genes seems as important as the ability to produce defined pathogenicity factors. In patients previously treated with antibiotics in hospital, *A baumannii* is a much more prevalent cause of pneumonia than in patients receiving no antibiotics.^{10 11}

Where do these multiresistant bacteria come from? We do not know if they are subpopulations with a predisposition towards resistance. We do know, however, that they often spread clonally and that this may have been facilitated by hospital designs that move patients closer together and rely on regular transfers of patients between different points of treatment. Cross infection is clearly a major contributor to the rise in resistance, and modern molecular typing techniques show widespread dissemination of single bacterial strains. As our knowledge of molecular biology increases and the bacterial genome projects advance, we may well find that certain multidrug resistant strains are quite distinct genetically from their sensitive counterparts. We will then be able to show whether our multiresistant bacteria evolve from strains commonly found in hospitals or whether the antibiotic blanket selects certain strains, which survive merely because of the propensity to carry resistance genes.

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Why can't GPs follow guidelines on depression?

We must question the basis of the guidelines themselves

The Hampshire depression project, published recently, was a large well designed randomised controlled study of teaching practitioners about the recognition and management of depression and using patient improvement as the outcome measure. Its results were disappointingly negative, failing to show any increase in recognition or patient recovery rates.¹ These findings herald the need for a major change in thinking about improving the management of depression in primary care.

Through the 1990s educational initiatives have been mounted to implement expert guidelines on

depression—based on the promising results of a study of educating 18 general practitioners in Gotland.² A two day course on recognising and managing depression given by psychiatrists was followed by increased antidepressant prescribing and decreased use of tranquillisers. Admissions for depression and the suicide rate both went down. The costs of the exercise were only 0.5% of the savings on admissions.

Subsequently, consensus guidelines on recognising and managing depression appeared in the United Kingdom.³ The Royal Colleges of General Practitioners and Psychiatrists mounted the “defeat depression”

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campaign, disseminating booklets and videotapes based on the guidelines. The Royal College of General Practitioners appointed a senior mental health education fellow to cascade education about depression down to general practitioners through regional mental health fellows and postgraduate tutors.

The Gotland study, however, was small and lacked a control group, and its benefits faded over two years.⁴ In contrast, the Hampshire depression project was large (26 out of 55 practice teams were given four hours' teaching followed by material tailored to their needs) and well enough designed to be confident of its negative results. These results conflict with the positive findings after more intensive training in recognition,⁵ but such intensive training cannot be delivered through our existing education systems. The results therefore question the whole approach of guideline based educational initiatives in depression. Indeed, we must now question the very basis of the guidelines themselves and their appropriateness in primary care.

A review of 45 clinical guidelines on depression⁶ concluded that all make essentially the same recommendations, based on the joint consensus statement.³ They recommend that practitioners seek cases of "major depressive disorder," a diagnosis which predicts response to antidepressants in most cases. Treatment is advised if patients have enough symptoms for long enough, even if there seems to be a cause for depression such as social problems. Most recommend tricyclic antidepressants as first line treatment, given in the equivalent of 125 mg/day of amitriptyline and continuing for four months after recovery.

Three problems exist with these recommendations. Firstly, the diagnosis is not easy to make in primary care. Depressive symptoms are distributed continuously in the population and can change quickly. Any cut off in the level or duration of symptoms is therefore somewhat arbitrary. As the severity of depression increases so more patients are diagnosed,⁷ but practitioners vary significantly in the threshold at which they label patients as "cases" needing treatment.

Secondly, many practitioners doubt the effectiveness of antidepressants in the face of social problems. The guidelines are based on a study suggesting that patients with a particular level of severity will respond to treatment, regardless of any apparent cause. In this placebo controlled trial of amitriptyline 125 mg/day, those with probable major depressive disorder responded but those with minor depression did not. No difference existed between those with endogenous and non-endogenous depression, and the authors concluded that treatment should be offered for probable major depression, regardless of demographic characteristics, history of depression, or endogenous features.⁸ However, this result derived from a post hoc analysis of subgroups and the study did not have the power to address the relative importance of severity and social factors in predicting treatment response. The importance of social factors is supported by other research showing that, in the short term, persistence of depression is associated with continuing social problems⁹ and recovery with a reduction in difficulties.¹⁰

Thirdly, even when doctors recognise depression and consider treatment appropriate, patients are often reluctant to accept drugs. Most of the British public

thinks that depression is due to adverse life events and that counselling should be offered.¹¹ Few think that it should be treated with drugs, and most think that antidepressants are addictive. This helps explain why patients take subtherapeutic doses of tricyclics and discontinue them after a few weeks. The advent of the selective serotonin reuptake inhibitors has increased the proportion taking therapeutic doses, but most patients do not continue treatment for the recommended duration.¹² This may explain the consistent finding that recognition of depression and drug treatment in primary care is not associated with a better outcome.¹³ The negative findings of the Hampshire depression project must be viewed in this context.

The uncertainty about the threshold for diagnosing and treating depression is understandable given our lack of knowledge of its natural course in primary care. Research is needed urgently into the outcome of depression over the whole range of severity and the impact of social factors in the medium to long term. The effectiveness of the serotonin reuptake inhibitors for minor depression has not been established in primary care, nor has the effectiveness of counselling. Yet without this information we cannot identify the threshold at which intervention should be offered. The experience of the 1990s has shown what can be achieved by guideline based education, but we should not expect such efforts to have a significant impact until we have improved the evidence base.

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TK has been paid fees for speaking at educational meetings by Pfizer, Lilly, and Lunbeck Pharmaceuticals. He is also doing research on depression in primary care with Chris Thompson, first author of the Hampshire depression study, though his research interest in this subject predated this collaboration.

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