Recurrent unipolar depression requires prolonged treatment†

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THE NATURE OF THE PROBLEM

Psychiatric disorder is now recognised as one of the greatest causes of human suffering. The burden to society of various diseases has been quantified recently using disability-adjusted life years (DALYs), a measure that expresses years of life lost to premature death and years lived with a disability of specified severity and duration. The burden of mental illness is second only to that of cardiovascular conditions in the developed world and when DALYs related to alcohol and drug misuse are included it is the largest single category (Murray & Lopez, 1997). Unipolar major depression currently imposes the second largest burden of any individual disorder in the developed world and, because of the decline in the incidence of ischaemic heart disease, may soon be the leading individual illness category (Murray & Lopez, 1997). Clearly, any improvements in the treatment of unipolar depression would produce great benefits in the health of the public.

The high disease burden of unipolar major depression is understandable when one considers the nature of the illness. Individual episodes are often prolonged, there is a high rate of progression to chronicity and relapse and recurrences are frequent. In addition, the illness is associated with pronounced psychosocial and physical impairments and a high suicide rate (Angst, 1999). Depression is a common condition, with an annual prevalence in Western countries of 3–10% and a life-time prevalence of approximately 17% (Angst, 1999), and it is often comorbid with other psychiatric problems and substance misuse. Unipolar depression frequently becomes chronic, with 12–20% of patients continuing to be fully symptomatic 2 years after initial diagnosis (Judd *et al*, 1997). The median number of episodes experienced is four (Anderson *et al*, 2000) and sufferers are subject to relapse and return of symptoms even after successful treatment (Surtees & Barkley, 1994). The long-term outcome of depression may differ with the setting, but recent evidence suggests that at least 85% of patients experience a relapse and that the high degree of recurrence occurs in community as well as hospital samples (Mueller *et al*, 1999).

TREATMENT WITH ANTIDEPRESSANTS

Although clinical trials of antidepressant treatments have shown the benefits of drug treatment, uncertainty remains about the most effective treatment of depression. An example of this is the recent debate in which the validity of clinical trials of antidepressants has been questioned and it has been suggested that antidepressants may be no more effective than active placebo treatments. Although more recent work supports the validity of clinical trials of antidepressants, this debate emphasises the need for constant re-examination of the evidence upon which we base clinical practice (Quitkin *et al*, 2000). Nor must we forget the role of psychotherapies; a recent study has shown the value of combining antidepressant medication and the cognitive–behavioural analysis system of psychotherapy in chronic depression (Keller *et al*, 2000).

Guidelines compiled by the British Association for Psychopharmacology (BAP) have comprehensively reviewed the evidence for treating depressive disorders with antidepressants (Anderson *et al*, 2000). These guidelines make use of an accepted classification of the categories of evidence and the strength of the recommendation made (Shekelle *et al*, 1999). Antidepressant treatment should be continued for 6 months after remission of symptoms, but the benefit of more prolonged treatment has not been demonstrated for non-selected groups of depressed patients, including those who are experiencing a first episode (Reimherr *et al*, 1998). However, relapse prevention has been shown for those patients with recurrent disorder for a number of different antidepressants, including imipramine (Frank *et al*, 1993), maprotiline (Rouillon *et al*, 1989) and paroxetine (Franchini *et al*, 1998). It seems likely that this effect of relapse prevention may be a property of all effective antidepressants, although in clinical settings an important difference may be that newer agents, such as the selective serotonin reuptake inhibitors, may be more likely to be given in a therapeutic dose (MacDonald *et al*, 1997).

TREATMENT OF RECURRENT UNIPOLAR DEPRESSION

The trial by Hochstrasser *et al* (2001, this issue) provides a timely reminder of the need for such prolonged treatment of recurrent unipolar depression and reinforces the evidence base and conclusions regarding prolonged treatment of recurrent depression in the BAP guidelines (Anderson *et al*, 2000). In this study the authors examined the prophylactic effect of the selective serotonin reuptake inhibitor citalopram in unipolar recurrent depression. The aim of the study was to compare the prophylactic efficacy of citalopram and placebo and also to determine the long-term tolerability of citalopram. In- and out-patients between the ages of 18 and 65 years, all of whom had to satisfy standardised diagnostic and severity criteria and have had two or more episodes of depression with at least one of these occurring within the past 5 years, were included in the study. Treatment consisted of citalopram (20–60 mg) for 6–9 weeks, with continuation treatment with citalopram for a further 15 weeks for patients responding to acute treatment. Patients then were assigned to double-blind maintenance treatment with citalopram or placebo for 48–77 more weeks, with the citalopram maintained at the dose that was efficacious in acute treatment. The main outcome measure was the eminently pragmatic one of time to recurrence of a new depressive episode. The results of the trial show that the time to recurrence of depression was significantly longer in the patients taking citalopram and that the advantage of citalopram over placebo was significant at all doses.

FUTURE DIRECTIONS

Although evidence continues to accumulate that selective serotonin reuptake inhibitors are effective and well tolerated during long-term treatment of recurrent unipolar

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depression, questions remain regarding long-term prophylactic treatment of recurrent depression. In this study, the difference in outcome between the citalopram- and placebo-treated groups was still evident at the end of the study period and the optimal duration of treatment therefore remains unclear. Finally, because most depressive illnesses will be treated in primary care, utilisation of currently effective treatments should be maximised by general practitioners, although recent attempts to foster this with guidelines have proved somewhat disappointing (Thompson *et al*, 2000).

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