British Journal of Psychiatry (1994), **165** (suppl. 26), 37–41

Antidepressants: Partial Response in Chronic Depression

JAN FAWCETT

Although most studies of chronic depression show significant improvements with antidepressants versus placebo, the average Hamilton Depression Rating Scale results attained in the active-treatment group range between 10 and 14, suggesting that many patients only partially responded and failed to reach premorbid levels of symptom remission. Studies on the fate of these patients suggest that they are much more vulnerable to relapse, work impairment and suicide. Thus, partial response may be one form of treatment resistance, falling between total failure of response in a minority of patients, and a tendency to relapse or recur despite adequate maintenance treatment. Further study is needed to address the problem of improving the quality of response and attempting to reduce the detrimental effects of depressive illness in terms of relapse and recurrence.

Major depression often demonstrates a chronic and/or recurrent course without treatment; therefore, treatment strategies have been expanded to include not only treatment of the acute episode but also continued and maintenance therapy to prevent future episodes. Antidepressant medication, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), lithium and atypical antidepressants, has proved clinically efficacious in patients with major depression. Furthermore, the newer selective serotonin reuptake inhibitors (SSRIs) and bupropion have shown comparable efficacy without some of the side-effects and toxicity associated with the TCAs and MAOIs (Song *et al*, 1993; Workman & Short, 1993). However, the success of these agents depends on the quality of the response elicited in the patients both during the acute treatment period and during the continuation and maintenance periods.

Up to 20% of patients may be resistant to treatment with antidepressant medications; however, the fact that perhaps another 20% to 30% of patients may only have a 'partial response' to treatment has not been emphasised in the treatment literature (Fawcett & Kravitz, 1985). Reviews of numerous studies of TCAs such as imipramine, and newer antidepressants including trazodone, bupropion and the SSRIs, have consistently defined response as a 50% reduction in Hamilton Depression Rating Scale (HDRS) scores (Workman & Short, 1993). This response occurs in 60–70% of patients treated with active medication, and is significantly better than responses to placebo in double-blind studies (Workman & Short, 1993). However, the average absolute HDRS scores attained in studies after 6–16 weeks of treatment range from approximately 10 to 16, suggesting that many of the patients treated have either not responded to treatment or have obtained partial but not total remission in response to treatment. Clinically, these patients often continue to suffer significant physical and social dysfunction. In a smaller number of studies, absolute HDRS cut-off scores between 6 and 8 were used, which are considered the normal range in healthy populations, or a total remission of depressive symptoms. Response rates in these studies range from 30–50% (Workman & Short, 1993). Therefore, because such a large proportion of patients do not appear to respond optimally to treatment, the clinical implications of a partial response to treatment are discussed.

Prevalence of partial response

Prien *et al* (1984) evaluated imipramine treatment in unipolar major depression and found that after 17 weeks of treatment and continuation treatment with imipramine, 48% of patients reached an HDRS of 7, which was the criterion for inclusion into the maintenance part of the study. The NIMH Collaborative Treatment Study, which compared interpersonal psychotherapy, cognitive therapy, imipramine (average dose of 185 mg/day) and placebo for 16 weeks of treatment, found an average 17-item HDRS response of 9.8. Only 40–60% of patients on imipramine reached an HDRS score of 7 or less, and the investigators concluded that, in general, patients were not sufficiently improved after 16 weeks of treatment to receive maintenance therapy (Shea *et al*, 1992).

In another study, Frank *et al* (1990) evaluated patients who had reached an HDRS of 7 or less after

a maximum of 20 weeks of combined imipramine and interpersonal psychotherapy treatment before receiving continuation and then maintenance treatment. Only 68% of their patients (excluding loss from medical illness or 'other reasons') were able to meet the criteria for inclusion into 17 weeks of continuation treatment; subsequently, only 56% were eligible to receive maintenance treatment (Frank *et al*, 1990). In addition, a study of fluoxetine, using a 21-item HDRS score of less than 12 as a criterion for inclusion into a continuation study, applied continuation treatment to 56% of patients, and only 48% were eventually eligible for maintenance randomisation (Montgomery *et al*, 1988).

These studies demonstrate that only 40–60% of patients receiving appropriate doses of antidepressants and structured supportive treatment for 12 to 20 weeks are attaining full remission of symptoms. Alternatively, 40–60% of these patients are left with a partial response to treatment.

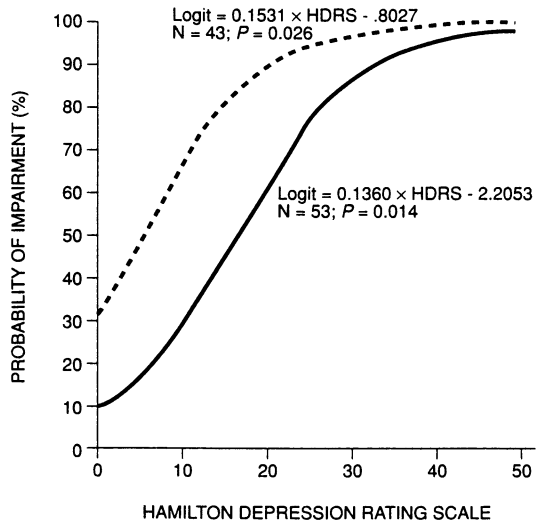

Fig. 1 Probability of functional (——) and affective (- - - -) work impairment as a function of observer-rated severity of depression. Curves are based on separate logistic regression analysis of 17-item post-treatment Hamilton Depression Rating Scale (HDRS). Reprinted with permission from Mintz *et al* (1992), *Archives of General Psychiatry*, **49**, 761–768; copyright 1992, American Medical Association.

Implications of partial response

Relapse rates

Four studies of the treatment of depression with antidepressants and/or psychotherapy have found that patients with a partial response have a significantly higher rate of relapse during the first six months following response. Mindham *et al* (1973) alluded to this observation in their study of 92 patients who had received TCAs during an acute treatment phase, and following response to therapy had been randomised to receive continuation treatment with TCAs or placebo. Of the placebo-treated patients who were not completely well at the end of the acute phase of treatment, 62% versus 33% of the placebo-treated patients who were well, experienced a relapse during the six-month study period.

Evans *et al* (1992) conducted a continuation therapy study comparing imipramine and cognitive therapy, and noticed that residual depression among the 44 out-patients predicted relapse ($P<0.01$). Similarly, Simons *et al* (1986), in their study comparing nortriptyline with cognitive psychotherapy, found that a Beck's Depression Inventory (BDI) score of greater than 10, which was used to define a partial response, at the beginning of the continuation treatment period was associated with a higher rate of relapse ($P<0.05$).

More recently, Montgomery *et al* (1991) evaluated maintenance treatment with fluoxetine, and stressed the importance of a symptom-free period before maintenance treatment is started, to reduce the likelihood of relapse in patients with partial antidepressant response. These studies support the idea that patients who do not attain a full remission (HDRS scores of less than 8) have a higher risk of relapse to a full episode of major depression compared with patients who reach full remission.

Functional impairment

In the Medical Outcomes Study, the physical and social dysfunction associated with depression was compared with five common medical illnesses such as arthritis, hypertension and diabetes (Wells *et al*, 1989). Patients with depression suffered from more impairment and spent more days in bed than patients with these common debilitating medical illnesses. Therefore, it is expected that patients with residual symptoms of depression will continue to experience some functional impairment.

Mintz *et al* (1992) analysed ten data sets of the treatment of depressed patients to examine the superiority of drug treatment versus placebo, using work impairment as an outcome measure. Of special interest is the curve developed by these investigators based on the study of Simons *et al* (1986) of nortriptyline versus cognitive therapy, which related

the probability of work impairment, based on three questions from the Weissman Social Adjustment Scale, to the severity of depressive symptoms (HDRS score: Fig. 1). For instance, patients having an HDRS score of 10 to 16 (the average response to antidepressant therapy in conventional studies) following 6–12 weeks of therapy have a 45–50% probability of work impairment. Those with a partial response to antidepressant therapy are clearly at a higher risk of work impairment than fully remitted patients. Additionally, the self-ratings of patients on the Weissman Social Adjustment Scale give even higher probabilities of functional impairment in relation to rising HDRS scores. The patient's response in attempting to cope with a work situation thus compromises their quality of life. The severity of residual depressive symptoms can also be extrapolated to the effect on the patient's interpersonal and family life.

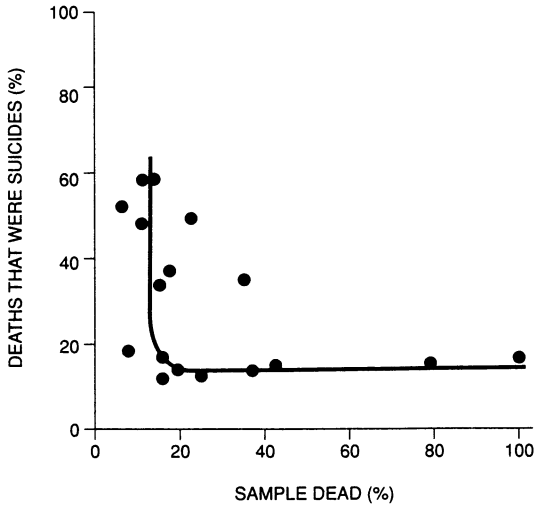

Fig. 2 Proportion of patients who commit suicide versus total deaths from all other causes in patients who were followed in antidepressant studies or naturalistic population surveys. Reprinted with permission from Guze & Robins (1970).

Risk of suicide

Guze & Robins (1970) summarised 17 studies of patients treated for depression and three population surveys to determine the proportion of deaths from suicide relative to the total number of deaths in the sample (Fig. 2). Patients in the sample followed for 5–6 years showed a suicide rate of 30–50%, whereas longer-term follow-up of 20 years showed a 15% suicide rate with respect to deaths from other causes. Fourteen of the 17 studies summarised by Guze & Robins (1970) were published before 1960 (i.e. before antidepressants were widely used). The question arises as to whether the same statistics, in terms of risk of suicide in a population of depressed patients, would be obtained since the introduction of the TCAs and subsequent generations of antidepressants.

An analysis of data from the Collaborative Study of Depression shows that after eight years, a cumulative 30% of all deaths were from suicide, with much higher rates of death from this cause in earlier years. This result appears to be similar to those summarised by Guze & Robins (1970) despite the introduction of antidepressants. Further follow-up will be necessary to show whether the same curve is obtained as in the analysis of Guze & Robins (1970). In the Collaborative Depression Study sample, the suicide rate during the first year of follow-up was 1%; rates in the entire sample during each subsequent year were 0.2% to 0.5% per annum.

Studies by Fawcett *et al* (1990) from the Collaborative Study of Depression have shown that high severity of several symptoms such as moderate alcohol abuse, anhedonia, psychic anxiety, panic attacks, diminished concentration and global insomnia are significant predictors of suicide in depressed patients (Table 1). In a prospective study of 954 patients with major depression, these clinical features were associated with a suicidal outcome within one year of a structured interview (Fawcett *et al*, 1990). Traditional predictors such as suicidal ideation (expressed to a clinician), history of prior suicide attempts, high clinical severity and intent of those attempts were not associated with suicide within one year of the intake interview. The symptoms severity predictors of suicide are the same as many of the target symptoms of pharmacological treatment. The persistence of these symptoms in patients with a partial response to treatment or their intensification as a result of a relapse, which is more likely to occur in partially responding patients, may be a major source of suicide risk in these patients.

Discussion

Based on this review, one can estimate that approximately 20% of patients with major depression fail to respond meaningfully to available antidepressant treatment. Furthermore, another 30% of treated patients achieve only a partial response, with many target symptoms still remaining in varying

https://doi.org/10.1192/S0007125000293276 Published online by Cambridge University Press

Table 1
Short-term predictors of suicide within one year in 954 patients with major affective disorders (Fawcett et al, 1990)

Symptom	Short-term probability (*P*-values)
Alcohol abuse	0.029
Loss of interest or pleasure	0.005
Psychic anxiety	0.012
Diminished concentration	0.028
Global insomnia	0.011
Panic attacks	0.024 (chi-square)

degrees of severity. The data reviewed here suggest that these patients have a higher rate of relapse than others. Even prior to relapse, these partially responding patients, with HDRS scores in the range of 10 to 16, are estimated to have a 50% probability of work impairment and a 65% probability of subjective distress associated with their interpersonal and family lives (Mintz *et al*, 1992).

Recent data further suggest that persistent severe symptoms of anxiety, anhedonia, insomnia, poor concentration and the presence of panic attacks appear to be associated with an acute risk of suicide. The implication is that the presence of these symptoms in partially responding patients or their intensification in a relapse would result in a higher risk of suicide.

Studies of the success of continuation and maintenance treatment in preventing relapse and recurrence of major depression respectively have demonstrated success, but have only included patients with a complete response (i.e. HDRS scores of $\leqslant 12$), while 40% to 50% of patients receiving 12–20 weeks of treatment failed to respond adequately to meet the criteria for continuation and maintenance therapy.

These estimates suggest that treatment resistance and partial response exists despite the progress that has been made in the treatment of depression. In fact, partial response could be seen as a form of treatment resistance given the hazards associated with partial response. A case could be made for reporting the outcome of antidepressant treatment studies in terms of the proportion of patients treated who reach a full remission (HDRS scores of 6 to 8), as opposed to only reporting improvement based on a 50% reduction in HDRS scores.

Furthermore, although new antidepressants appear to have distinct advantages in terms of side-effects, overdose toxicity hazards, and improvement in patient acceptance, none of these agents has as yet demonstrated a response profile superior to that of traditional TCAs in terms of the percentage of patients reaching a full remission (Song *et al*, 1993). Recognising the progress that has been made, perhaps it is now time to focus both on the problem of treatment resistance and on the development of treatment strategies or agents with novel actions that might benefit those patients who partially respond to presently available treatment.

A number of more aggressive treatment strategies are available, including MAOIs (Quitkin *et al*, 1989; McGrath *et al*, 1993), potentiation strategies with lithium (Heninger *et al*, 1983; de Montigny *et al*, 1983; Cowen *et al*, 1989; Schopf, 1989; Fontaine *et al*, 1991), hormones such as triiodothyronine (Extein & Gold, 1988) or stimulants (Fawcett *et al*, 1991). These should be further investigated for patients who manifest treatment resistance, either totally or partially, because of the risk of significant impairment and even suicide. Medications with dopaminergic activities including bupropion and selegilene are used for some treatment-resistant patients, but further development of dopaminergic active medications may allow some forms of treatment-resistant depression to be overcome (Kapur & Mann, 1992; Serra *et al*, 1992).

Complacency in our capacity to treat major depression is clearly not warranted by the present state of the art. The success of clozapine in improving schizophrenic patients who are non-responsive to conventional neuroleptics is an example that should encourage us in our pursuit of not just more antidepressant medications (Kane *et al*, 1988), but agents that will actually produce a higher percentage of full remission in the patients we treat.

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Jan Fawcett, MD, Professor of Psychiatry, Rush-Presbyterian-St Luke's Medical Center, 1725 West Harrison, Suite 955, Chicago, Illinois, USA