The Pharmacotherapy of Depression

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Over the years, most of the research into the pharmacotherapy of major depression has focused on the treatment of the acute depressive episode. There is a vast literature which documents the efficacy of the tricyclic antidepressants, monoamine oxidase inhibitors and, more recently, the serotonin reuptake inhibitors in the acute management of unipolar major depressive disorder. Recently however, there has been an effort to define particular subtypes of major depression which may predict response to specific classes of antidepressants. Second, there has been an increasing recognition of the chronic and recurrent nature of unipolar affective illness so that studies have addressed issues such as the longitudinal natural course of the disorder and long term pharmacotherapy to prevent relapse and recurrence of episodes.

The antidepressant treatment of major depression has been divided into three components (Prien and Kupfer 1986; Quitkin et al 1976). The first, acute treatment, involves the use of antidepressants to control the acute symptoms. The second, continuation treatment, is predicated on the assumption that antidepressants suppress depressive symptoms instead of correcting the underlying depressive disorder. It therefore, involves the continuation of antidepressant therapy after acute treatment so as to prevent reemergence of symptoms from the present episode (Prien and Kupfer 1986; Quitkin et al 1976). The last component, maintenance therapy, involves long term administration of antidepressants to prevent future episodes after the current episode has resolved (NIMH/NIH Consensus Development Conference Statement 1985). Although conceptually distinct, these three components of treatment are often difficult to distinguish in clinical practice. Nonetheless, in this discussion, each will be considered separately so as to allow for a critical evaluation of current issues pertinent to the acute and long term management of patients with unipolar major depressive illness.

Acute Treatment

It is widely accepted that approximately 60% to 70% of acute major depressive episodes will respond to intensive antidepressant treatment (Klerman 1990). A large number of clinical drug trials have documented this to be the case for a variety of heterocyclic antidepressants, monoamine oxidase inhibitors and the new generation antidepressants including the serotonin reuptake inhibitors. It has also been generally accepted that, for an acute episode, all antidepressants have roughly comparable efficacy and differ largely in their side effects (Joffe 1986). However, two major issues have recently received attention in the literature. First, Keller et al (1986) recently described the antidepressant treatment received by subjects at five university centres participating in the National Institute of Mental Health Collaborative Study on the Psychobiology of Depression. They observed that, in the first 8 weeks of treatment, 31% of 250 inpatients and 53% of 88 outpatients received no or very low levels of pharmacotherapy. Furthermore, only 49% of the inpatients and 19% of the outpatients received an equivalent of 200 mg of imipramine per day, sustained over a minimum period of 4 weeks. They also found that, the site of treatment, and not clinical or demographic characteristics was the best predictor of the level of antidepressant therapy. Although the generalizability of these findings are uncertain, they are of some considerable concern, as one would expect optimum antidepressant treatment in university-affiliated centres. It raises the issue whether standards of clinical
practice for the acute treatment of depression should be established (Kupfer and Freedman 1986), especially since inadequate acute treatment of depression is associated with increased psychosocial and medical morbidity (Klerman 1986, as well as poor long term prognosis (Goethe et al 1980; Keller et al 1984). There are numerous practical difficulties in establishing optimum dosage and duration of acute antidepressant treatments and these have been extensively discussed by Kupfer and Freedman (1986). Nonetheless, optimum treatment may also involve the early treatment of an acute depressive episode (Kupfer et al 1989). Kupfer and colleagues (1989) examined whether early treatment intervention had any effect on duration of episode in 45 patients with recurrent major depressive disorder. They observed that the speed of antidepressant response was not greater with early intervention; however, the duration of the episode was substantially reduced, by almost 50% by rapid intervention. Although these observations were made in a highly selected group of patients receiving combined pharmacotherapy and interpersonal psychotherapy, they provide preliminary support for the advantages of early intervention in patients with acute major depression.

The second issue concerning acute treatment relates to whether particular clinical subtypes of major depression may predict response to certain classes of antidepressants. Several studies have shown that panic attacks in females with major depression may predict response to monoamine oxidase inhibitors as compared with tricyclic antidepressants (Quitkin et al 1990; Liebowitz et al 1988). Quitkin and collaborators (1988; 1989) have defined an atypical depressive syndrome which is preferentially responsive to monoamine oxidase inhibitors. They defined atypical depression as the presence of mood reactivity plus one or two of the following four symptoms: hyperphagia, hyperactivity, leaden feelings and rejection sensitivity. In a large study, involving 120 depressed patients, they showed that phenelzine was significantly better than both imipramine and placebo in treating patients with this form of atypical depression. Furthermore, they showed that the atypical depressive syndrome predicted response to phenelzine regardless of the presence of a concurrent diagnosis of panic disorder. Their data are of considerable interest because it provides strong evidence for the presence of a specific subtype of major depression which predicts response to a particular class of antidepressants. It would be of interest to determine how the new generation antidepressants, such as the serotonin reuptake inhibitors, would compare to the monoamine oxidase inhibitors in the treatment of this group of subjects with atypical depression.

Clinical lore suggests that unipolar depression is an illness from which most patients tend to recover with a complete return of premorbid function. Furthermore, it has been accepted that episodes are self-limited, lasting an average of six to nine months, and that approximately one-half of patients do not have a recurrent illness. However, recent studies and clinical experience emphasize the chronic and recurrent nature of unipolar affective illness (NIMH/NIH Consensus Development Conference Statement 1985; Belsher and Costello 1988). Consequently, more attention has been paid to continuation and maintenance therapy of the depressive disorders.

**Continuation Treatment**

Several studies have examined the outcome of patients with major depression. As Keller and Shapiro (1981) note, naturalistic follow-up studies are required to examine recovery from depression as controlled studies of drug treatment do not allow for adequate assessment of recovery and relapse nor do they allow for precise determination of episode length. Five clinical naturalistic studies, with follow-up ranging between 10 and 18 months, have reported recovery rates ranging from 31% to 89% (Cadoret 1980; Morrison et al 1973; Paykel and Dienelt 1971; Schapira et al 1972; Winokus et al 1969). The wide variance in results from the studies are due to several methodological limitations including the poor definition of depressive illness, the failure to define recovery by the presence or absence of specific symptom criteria, rather than by measures of depression severity, and the retrospective design employed in several of these studies (Cadoret 1980; Morrison et al 1973; Paykel and Dienelt 1971; Schapira et al 1972; Winokus et al 1969). Keller and collaborators (1982) addressed many of these methodological concerns in a prospective naturalistic study with a one-year follow-up. Using regression models and life tables, they observed that only 50% of patients recovered one year after the onset of their major depressive episode. If recovery was evaluated from the time of entry into the study then 74% of subjects had recovered at one year. Their data suggest that many patients have a protracted course of their depression and that a substantial minority of patients have a chronic course of illness (Keller et al 1984; Keller and Shapiro 1981; Keller et al 1982). Keller et al (1982) also reported that clinical issues such as long duration of episode before entry into the study, double depression and comorbidity, particularly with alcohol and drug abuse and anxiety disorders, were clinical predictors for nonrecovery. The data from these clinical studies have recently been confirmed in a community sample. Sargeant and collaborators (1990) reevaluated 423 subjects with DSM-III major depression as determined in the epidemiologic catchment area study after one year. They found that 23.6% of subjects met the criteria for major depression and that the clinical predictors for nonrecovery were similar to those in the clinical studies (Keller et al 1984; Keller and Shapiro 1981). Although the conclusions from the epidemiologic study are limited by the cross-sectional assessment of subjects at two points in time, the findings are remarkably similar to those reported in clinical studies.
The above mentioned clinical and epidemiological studies strongly support the need for continuation therapy in patients with major depression. However, the duration of continuation therapy remains poorly defined (Prien and Kupfer, 1986). Although it has been suggested that this phase of treatment should continue for anywhere up to 12 months, this may be unnecessarily long in many cases (Prien and Kupfer 1986). Furthermore, the side effects of the various classes of antidepressants may become a major issue with prolonged continuation therapy which may lead to poor compliance with therapy. The considerable variance in estimates of episode length from earlier studies of the course of affective illness are not helpful in determining the duration of continuation therapy. Furthermore, the potentially promising utility of biological markers such as escape from dexamethasone suppression and blunting of the TRH test (Prien 1983; Targum 1984) in confirming the end of an episode remain to be established. Nonetheless, there is strong empirical evidence in support of the efficacy of continuation therapy in depressive illness.

In a review (Prien and Kupfer 1986) of 6 studies (Seager and Bird 1962; Mindham et al 1973; Prien et al 1973; Klerman et al 1974; Coppen et al 1978; Stein et al 1980) depressed patients assigned to placebo after antidepressants were used to control their acute symptoms were twice as likely to relapse compared with patients receiving active continued treatment. Only one study to date, of which I am aware, has examined the required duration of continuation therapy (Prien and Kupfer 1986). Prien and Kupfer (1986) examined the frequency of relapse in 72 patients with unipolar depression who were randomly assigned to either placebo or active treatment after stabilization of their acute depressive symptoms. They observed that frequency of relapse remained consistent and approximated that of active treatment, when patients were assigned to placebo after being symptom free for at least 16 weeks. In those subjects assigned to placebo before a 16-week symptom-free period, the frequency of relapse was significantly higher.

Their study suggests that continuation therapy should last at least 16 weeks beyond complete symptom remission in order to reduce the likelihood of relapse. If their findings are replicated in future studies, they will provide important information about what constitutes adequate, but not unnecessary, continuation therapy to improve the long-term prognosis of these disorders.

Maintenance Treatment

Early studies reported that multiple episodes occurred in anywhere from 13% to 54% of unipolar depressed patients. These studies have been extensively and critically reviewed by Zis and Goodwin (1979). The wide variability in the frequency of recurrence in unipolar affective disorder has been attributed to several possible factors in studies to date including the duration of the observation period, the means of defining a recurrence, the counting of the number of episodes prior to the index episode and patient differences, particularly in view of the heterogeneity of unipolar depression (Zis and Goodwin 1979). Recently, the recurrent nature of unipolar affective illness has been much more appreciated and it is estimated that between 50% and 85% of patients with major depression will have at least one more episode of illness in their lifetime (NIMH/NIH Consensus Development Conference Statement 1985). Several factors have been identified as increasing the risk of recurrence. These factors, largely derived from naturalistic follow-up studies include concurrent dysthymic disorder, comorbidity with substance abuse and anxiety disorders, older age of onset of the illness and the number of previous episodes prior to the index episode (NIMH/NIH Consensus Development Conference Statement 1985). With regard to risk factors for recurrence, the study of Frank and colleagues (1989) is of particular interest. They evaluated 74 patients with recurrent unipolar depression who discontinued medication after 20 weeks of continuation treatment. They found that the mean period of time for 50% of subjects to have a recurrence was 21 weeks and that this was significantly increased by treatment with interpersonal psychotherapy. They further observed that there were no clinical, demographic or pharmacological correlates of recurrence in contrast to the findings of the naturalistic studies. The sample in the Frank et al study was highly selected so the generalizability of these findings to usual clinical populations may not apply; however, they raise the issue of an inherent biological predisposition to relapse, regardless of clinical, demographic or pharmacologic factors. These investigators also found preliminary evidence that shortened REM latency may be a candidate for one of the biological risk factors for recurrence in unipolar depression. There is no doubt that further study is required to identify potential biological factors which may predispose an individual to recurrence of affective episodes.

Over the years, there has been an increased research effort to evaluate the efficacy of pharmacotherapy in the prevention of recurrence of depressive episodes. To date, three studies have shown that lithium is superior to a heterocyclic antidepressant in the prevention of recurrence (Coppen et al 1976b; Kane et al 1982; Prien et al 1973). On the other hand, two studies have reported that lithium and imipramine have comparable efficacy in the prevention of recurrence (Glen et al 1981; Prien et al 1984) whereas one study has shown imipramine to be superior to lithium in long-term maintenance treatment of unipolar depression (Frank et al 1990). The difference in conclusions reached by these various studies may be explained by several factors including, as Prien et al (1984) have noted, differences in the patients studied. In those reports in which lithium was shown to be superior to a cyclic antidepressant, patients were more stable at the point of entry into the study and had been episode free for at least 7 to 12 months. In the
NIMH collaborative study (Priem et al 1984), imipramine was found to be superior to lithium in preventing depressive recurrences in the overall sample of 88 unipolar patients followed for 2 years. However, the success of prophylaxis was strongly influenced by the severity of the index episode. In those cases in which the index episode was severe, imipramine was significantly more effective than lithium, but in those in which the index episode was of moderate severity, there was no significant difference in the efficacy of the 2 treatments. This study (Priem et al 1984) was also the only one to evaluate the effectiveness of combined treatment with lithium and imipramine in the prevention of recurrence. Although the combination was more effective than lithium alone and placebo, it was no more successful than treatment with only imipramine. Although these various studies have established the efficacy of lithium and antidepressants in the prevention of recurrence (Coppen et al 1976; Kane et al 1982; Priem et al 1973; Glen et al 1981; Priem et al 1984; Frank et al 1990), a substantial proportion of patients still have recurrent episodes despite active treatment. For example, in the British Medical Research Council study of Glen et al (1981), successful prevention of recurrence occurred in only 32% of the amitriptyline-treated group and 30% of the lithium-treated group. Furthermore, in the NIMH collaborative study (Priem et al 1984) only about 50% of subjects had successful prophylactic response to imipramine at 2 years follow-up. In both these studies, the dose of tricyclic used for maintenance treatment was lower than that employed for management of the acute episode. This conformed with the widely accepted practice that lower doses of antidepressant drugs are required for maintenance as compared with acute treatment (Klerman 1990). Because of the high recurrence rates despite active maintenance treatment in these various studies the findings from a recent study are of particular interest. Frank et al (1990) reported their findings from the 3-year outcome of the Pittsburgh Maintenance Therapies in Recurrent Depression Study involving 128 subjects receiving maintenance treatment with various combinations of imipramine and interpersonal psychotherapy. They observed that active treatment with imipramine was highly successful in the prevention of recurrence. Furthermore, they also observed a modest effect of interpersonal psychotherapy in the prevention of relapse. While the comparative efficacy of pharmacotherapy and psychotherapy will generate considerable debate, of particular note, they reported that, in the patients treated with imipramine alone, approximately 78% had no recurrence after 2 years. This is in contrast to the findings of Priem et al (1984) who observed an approximately 50% success rate with imipramine after 2 years. The two patient populations employed in these studies differed, particularly as subjects with concurrent dysthymia, a risk factor for relapse (NIMH/NIH Consensus Development Conference Statement 1985), were excluded from the Pittsburgh study. However, both samples had a comparable frequency of relapse prior to the index episode. In the Pittsburgh study, the investigators had deliberately maintained the dose of imipramine at levels comparable to that used for the treatment of acute symptoms so they had not reduced the dosage for maintenance therapy as was done in the NIMH collaborative study (Frank et al 1990). They concluded (Frank et al 1990) that the increased success rate was likely due to maintenance of aggressive treatment with imipramine. Although their data are convincing, these two studies (Priem et al 1984; Frank et al 1990) cannot be directly compared as the patients in the Pittsburgh study had received combined pharmacotherapy and psychotherapy for a substantial period of time.

The studies on the prevention of recurrence in unipolar depression suggest that both lithium and cyclic antidepressants may be effective in particular patients. The decision whether to choose lithium or imipramine may depend on the clinical situation. Antidepressants are generally used for management of acute symptoms and therefore, are convenient for prophylaxis. Based on the studies to date, they should be preferred over lithium in patients who have had a severe depression and should be used in doses similar to those employed during the acute episode. Lithium may offer an advantage in those patients who are intolerant of antidepressants and they also may offer greater protection against the switch into mania which occurs in up to 10% to 15% of patients initially diagnosed as suffering from unipolar depression (NIMH/NIH Consensus Development Conference Statement 1985).

CONCLUSIONS

In this paper, I have reviewed the various components of treatment of unipolar affective illness. Further research and clinical focus is required in all three components of treatment. As far as acute treatment is concerned, future studies should address whether specific clinical subtypes of major depression are particularly responsive to various classes of antidepressants. Although preliminary data in this regard are intriguing (Quitkin et al 1990; Liebowitz et al 1988, Quitkin et al 1988; Quitkin et al 1989), further studies are required. Furthermore, future studies should also take into consideration the role of new generation antidepressants, such as the serotonin reuptake inhibitors in these various subtypes of depression.

There is greater appreciation for the chronic and recurrent nature of unipolar depressive illness (NIMH/NIH Consensus Development Conference Statement 1985). Further studies are required to define the extent and duration of continuation therapy although preliminary data suggest (Prien and Kupfer 1986) that at least 4 to 5 months of treatment are required beyond suppression of acute symptoms in order to reduce the risk of relapse. As far as prophylactic treatment is concerned, the efficacy of lithium
as well as the various antidepressants have been established (Coppen et al 1976; Kane et al 1982; Prien et al 1973; Glen et al 1981; Prien et al 1984; Frank et al 1990). However, more specific guidelines for the use of the antidepressants will have to be developed. For example, the notion that similar doses of antidepressant drugs to that used for acute treatment may substantially increase the success of maintenance treatment, requires replication in future studies. The role of particular types of psychotherapy alone or in combination with antidepressants also requires further attention (Frank et al 1990).

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