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Long-Term Antidepressant Treatment

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ABSTRACT *~ Major depressive disorder (MDD) is a common and costly illness. Recent research suggests that MDD is a lifelong condition for many patients. This has stimulated researchers to identify risk factors associated with an increased frequency of relapse and recurrence of major depression. One of the most important of these risk factors is an incomplete response to acute treatment. These data have led investigators to pursue techniques that enhance the acute response of patients to therapy, and study whether long-term treatment with antidepressants may prevent relapse and recurrence of MDD. Data from these trials suggest that continuation and maintenance treatment of MDD confers some protection against deteriorating back into an episode after acute treatment and against developing another episode of MDD.* Psychopharmacology Bulletin. *2002;36(suppl 3):26–38*

Introduction

Major depressive disorder (MDD) has a lifetime prevalence of 7% to 12% among men and 20% to 25% among women 18–54 years of age.[1-3] Depression is ubiquitous and has similar prevalence rates throughout the industrialized world. Individual episodes of depression usually last 3–12 months (median duration, ~6 months). Although the etiology of depression is not known, a complex combination of biological, genetic, and environmental factors seems to influence the onset and course of this syndrome. Factors associated with a more complicated course of treatment and worse prognosis include greater severity of depressive symptoms, longer duration of depressive symptoms, the presence of comorbid medical illnesses, the presence of comorbid psychiatric disorders (including personality disorder), a family history of mood disorder, and incomplete recovery from a previous episode.[4-6]

The cardinal features of major depressive disorder are the presence of either depressed mood (feeling down, irritable, or apprehensive) or a loss of pleasure in typically enjoyable activities most of the time for at least 2 weeks. Other signs and symptoms of MDD include appetite disturbance (hyperphagia or decreased appetite), unintentional loss or gain of weight, hypersomnia, insomnia,

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psychomotor retardation or agitation, decreased energy or fatigue, loss of concentration, feelings of worthlessness or inappropriate guilt, and thoughts of death or suicide.[4]

There are three major subtypes of MDD: psychotic, melancholic, and atypical. Patients with psychotic features display delusions or hallucinations that are typically worse during the first 6 months of the episode, reducing in intensity over time. Patients with melancholic features have diurnal variation, weight loss, and problems with insomnia, but seem to be responsive to pharmacotherapy and electroconvulsive therapy. Patients with atypical features experience reverse neurovegetative signs and symptoms like hypersomnia and hyperphagia. They tend to be more rejection sensitive. These patients tend to respond better to selective serotonin reuptake inhibitors and monoamine oxidase inhibitors.

Phases of Treatment

There are three types of treatment options commonly employed for patients with MDD: pharmacotherapy, psychotherapy, and combined therapy. (Somatic treatments including electroconvulsive therapy, light therapy, vagus-nerve stimulation, and transcranial magnetic stimulation are used in a minority of patients and most commonly in research settings.) Once a patient and physician agree upon a treatment option, the patient enters the acute treatment phase. This phase usually lasts at least 6–12 weeks, but may take many months in complex cases. Although clinicians and patients have often previously accepted any response to therapy as a success for acute treatment, newer data suggest that the true goal should be remission of symptoms. The continuation phase begins once the patient has responded (or preferably remitted) with the help of acute treatment. The goal during this phase is to prevent relapse (a return of symptoms of the major depressive episode). This phase is usually conceptualized as lasting 3–6 months.

The third phase of treatment is maintenance therapy. This may continue from approximately 6–9 months after a first episode of depression to many years for patients with three or more previous episodes of MDD. The goal of this phase is to prevent a recurrence (a new episode of major depression) and preferably to provide continuing sustained remission. Attainment of initial remission and then sustained remission is the best way to prevent depression-related morbidity.[7]

Definitions of Treatment Outcomes

Previously, inconsistencies in the definitions of outcomes have complicated research investigating treatment interventions for MDD. However, more widely accepted definitions for outcomes commonly

associated with the treatment of MDD have emerged in recent years. The five most commonly used terms to define outcomes are response, remission, recovery, relapse, and recurrence. Response is generally defined as scores indicating a ≥50% decrease from baseline scores on the 17-Item Hamilton Rating Scale for Depression (HAM-D), or the Montgomery-Asberg Depression Rating Scale (MADRS).

Remission is generally defined as a HAM-D score ≤7, although other definitions such as a Clinical Global Impressions-Improvement scale (CGI-I) score of 1 (very much improved) have been used in clinical studies. Some researchers have suggested that remission should be defined as the complete remission of all signs and symptoms of depression for a minimum of 2 weeks (L. L. Judd, MD, oral communication, September 1999).

Recovery is defined as an asymptomatic period lasting at least 6 months following an episode of depression. A relapse occurs when symptoms severe enough to meet syndromal criteria for MDD return within the first 6 months following response or remission of an episode. A recurrence is defined as the return of depressive symptoms at least 6 months following recovery from a prior episode of MDD (ie, a new episode of depression).[8,9]

The General Acceptance of Treatment Standards

Many international societies and an increasing number of regulatory agencies now recognize the need for continuation and maintenance treatment for MDD. Acceptance of these concepts signifies a shift in our conceptualization away from considering MDD to be an acute illness, such as a bacterial infection, toward an understanding that MDD is a chronic condition for many. The Agency for Health Care Policy and Research, now called the Agency for Healthcare Research and Quality (AHRQ) recognizes three initial objectives of treatment: (1) to reduce and ultimately remove all signs and symptoms of the depressive syndrome; (2) to restore occupational and psychosocial function to that of the asymptomatic state; and (3) to reduce the likelihood of relapse and recurrence.[8] The AHRQ guidelines now suggest that treatment of an uncomplicated episode of MDD continue for a total of 9 months. The American Psychiatric Association treatment recommendations for patients with MDD emphasize maintenance-phase treatment to prevent relapse.[10] In 2000, the depression treatment guidelines of the British Association for Psychopharmacology were revised to acknowledge that remission is a key goal for treatment and that many patients will require long-term treatment for their MDD.[11] Guidelines from the Canadian Psychiatric Association and the Canadian Network for Mood

and Anxiety Treatments specify that the goals of treatment are remission of symptoms and a return to premorbid social functioning.[12]

Relapse Prevention Studies

Relapse of depression is defined as the return of symptoms meeting the full syndromal criteria within 4–6 months of an acute treatment response to an episode of MDD. The importance of continuation treatment in preventing relapse was first documented by Prien and Kupfer.[13] They determined that 40% to 60% of individuals with MDD will relapse within 8 weeks of precipitously decreasing antidepressant treatment after an acute response. These findings triggered the development of studies designed to investigate the efficacy of continuation antidepressant treatment in preventing relapse. The section below describes a representative, but by no means exhaustive, number of these trials.

The first controlled continuation phase study to evaluate the safety and efficacy of bupropion sustained release (SR) in decreasing the risk of relapse for responders to acute treatment was published in 2002.[14] Patients were treated with open-label bupropion SR (300 mg/day) for 8 weeks; responders entered a 44-week, randomized, double-blind phase. Relapse in this study was defined as the reemergence of symptoms meeting criteria for MDD. Of the 423 randomized patients (213 placebo and 210 bupropion), 417 patients were included in the efficacy analyses. Statistically significant separation between bupropion SR and placebo began at double-blind week 12 and continued throughout the remainder of the study ($P<.05$). The median time to relapse in the placebo group was 24 weeks compared with 44 weeks in the bupropion SR group. This study suggests that continued bupropion SR treatment is effective in decreasing the incidence of relapse among patients with major depressive disorder.

Kunz[15] studied the efficacy of venlafaxine extended release (XR) in the prevention of relapse in patients with MDD. Patients who responded to 8 weeks of open-label treatment with venlafaxine XR were randomly assigned to double-blind continuation treatment with venlafaxine XR or with placebo for up to 6 months. Relapse was defined as a score of ≥4 on the Clinical Global Impressions-Severity scale (CGI-S). Of the 401 patients who completed the 8-week acute treatment phase, 328 entered the relapse prevention phase and 318 (161 venlafaxine XR and 157 placebo) were included in the efficacy analyses. Relapse rates for patients treated with venlafaxine XR were 18.8% at 3 months and 28.2% at 6 months, compared with 43.6% at 3 months and 52.3% at 6 months for placebo-treated patients ($\chi^2=18.6$, $P<.001$ at 6 months). During the trial, 51 patients in the venlafaxine XR group and

73 patients in the placebo group discontinued treatment, but twice as many patients in the placebo group (42%) compared with the venlafaxine XR group (24%) discontinued due to lack of efficacy ($P<.001$).

Thase and colleagues[16] published the results of a double-blind, placebo-controlled relapse prevention study of mirtazapine. Fully remitted patients (N=178) were randomly assigned to 40 weeks of double-blind treatment with either mirtazapine (15–45 mg/day) or placebo. Relapse was defined as any one of the following: (1) HAM-D score ≥18; (2) HAM-D scores ≥15 at two consecutive visits; or (3) suicide or attempted suicide. The relapse rates were 19.7% (15/76) for the mirtazapine group compared with 43.8% (35/80) for the placebo group ($\chi^2=10.48$, $P=.001$). Again, these results suggest that continuation treatment with mirtazapine is effective in preventing relapse of MDD.

Robert and Montgomery[17] conducted a continuation treatment study with citalopram. In an open-label phase of the trial, 226 of 391 patients responded to citalopram treatment by week 8 (total score 12 or less on the MADRS). Seventy-four patients were randomized to placebo-treatment and 152 patients were randomized to continue citalopram treatment during the 24-week continuation phase. Relapse was defined as an MADRS total score ≥25. Of the patients receiving citalopram, 14% (21/152) relapsed compared with 24.3% (18/74) of the patients receiving placebo ($P=.04$). The results of this study are consistent with those of other continuation antidepressant studies and support the preliminary analysis by Prien and Kupfer,[13] suggesting that full-dose continuation treatment is more effective than placebo treatment in preventing relapse of MDD.

Recurrence Prevention Studies

A recurrence is defined as a new episode of depression occurring 6 or more months after recovery of a previous episode. Maintaining treatment beyond the 4–6 month continuation period has been shown to significantly reduce the risk of recurrence (ie, a new episode). Analysis from the National Institute of Mental Health (NIMH) collaborative study of the psychobiology of depression found that the incidence of depression recurrence after recovery increases over time; the rate of recurrence was 13% at 6 months, 28% at 1 year, 43% at 2 years, 62% at 5 years, 75% at 10 years, and 87% at 15 years.[18] The number of previous episodes of depression was positively associated with less time between episodes (ie, the greater the number of episodes, the shorter the time to recurrence). Other risk factors that increase the rate of recurrence have been identified (Table).[19] It has been suggested that patients with these risk factors might benefit from prophylactic or continuous maintenance

therapy. There have been a number of double-blind, placebo-controlled discontinuation studies investigating prevention of recurrence.

The importance of maintenance treatment for recurrent MDD was first dramatically demonstrated by the work of Frank and colleagues in a 3-year NIMH-funded trial.[20] During the acute phase of this trial, 230 patients received combined treatment with imipramine and interpersonal psychotherapy (IPT). Of these, 157 attained a HAM-D score ≤7 and a Raskin Severity of Depression (RSD) score ≤5 for 3 consecutive weeks, and entered a 17-week continuation treatment phase. One hundred twenty-eight patients had a sustained response (HAM-D score ≤7 and an RSD score ≤5) and continued on a stable dosage of imipramine. These patients were randomly assigned to one of five different maintenance treatment strategies: (1) maintenance IPT (IPT-M); (2) IPT-M with active imipramine; (3) IPT-M with placebo; (4) imipramine alone; (5) placebo alone. The primary efficacy analysis was to determine whether interpersonal psychotherapy alone or in combination with imipramine would be more effective than placebo in the prevention of recurrence. The overall outcome of this trial demonstrated that full-dose maintenance therapy with imipramine (either alone or in combination with IPT) was more effective than placebo discontinuation in preventing recurrence. Although patients who continued to receive IPT were less likely to have a recurrence than those who discontinued from both pharmacotherapy and IPT, this result was not clinically or

TABLE

RISK FACTORS ASSOCIATED WITH RELAPSE OR RECURRENCE OF DEPRESSION

- Comorbid psychiatric illness
- Severe index episode
- Increased number of episodes
- Long duration of an episode
- Increased severity of an episode
- Comorbid medical illness
- Seasonal pattern of depression
- History of inadequate treatment response
- Family history of mood disorders
- Incomplete recovery from an episode
- Neurotic personality style
- Very early onset of illness
- Onset over the age of 60
- Dysthymic disorder
- Poor medication adherence

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statistically significant. This study has been the impetus for the development of maintenance trials of antidepressant medication.

Kunz[15] conducted a randomized, double-blind, placebo-substitution trial designed to evaluate the efficacy and safety of prophylactic venlafaxine treatment in outpatients with recurrent MDD. Patients who responded to treatment with venlafaxine (100–200 mg/day) and who remained relapse-free during a 6-month open-label period were randomly assigned under double-blind conditions to continue receiving venlafaxine for up to 12 months or to switch to placebo. The primary efficacy outcome was the number of patients who had a recurrence of depression (CGI-S score ≥4).

Two hundred eighty-six patients completed the 6-month open-label treatment period and met remission criteria. Two hundred thirty-five patients entered the recurrence prevention phase and 225 (109 venlafaxine and 116 placebo) were included in the analyses. The rate of recurrence was 22% for the venlafaxine-treated patients and 55% for the placebo-treated patients ($P<.001$) at 12 months. Thus, the data suggest that continued treatment with venlafaxine is more effective in preventing recurrence of depression than placebo. These data are also of interest because they support the findings of Frank and colleagues[20] that a significant number of successfully treated patients will relapse when antidepressant therapy is discontinued.

In another large recurrence-prevention study published by Gilaberte and colleagues,[21] patients with a history of recurrent depression who met criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition-Revised (*DSM-III-R*) for current major depression and responded to 32 weeks of open-label fluoxetine treatment were randomly assigned to receive fluoxetine (20 mg/day) or placebo for an additional 48 weeks. The primary outcome measure was a recurrence of MDD defined specifically as: (1) meeting *DSM-III-R* criteria for major depression; and (2) having a HAM-D score ≥18 or a CGI-S score ≥4, or both, for at least 2 weeks. Of the 140 patients who entered the double-blind maintenance treatment phase, 120 were included in the efficacy analyses. The fluoxetine-treated patients were less likely to have a recurrence than placebo-treated patients (22.1% versus 49.1%; $P=.0002$). Fluoxetine treatment was also associated with a much longer symptom-free period (295 days) than placebo treatment (192 days). This active treatment not only decreased the number of recurrences but increased the length of time patients stayed well.

Hochstrasser and colleagues[22] investigated the efficacy of citalopram treatment in the prevention of recurrence of MDD. Four hundred twenty-seven patients who had a *Diagnostic and Statistical Manual of*

Mental Disorders, Fourth Edition diagnosis of MDD, an MADRS score ≥22, and at least two prior episodes of depression (one within the past 5 years) entered a 6–9 week acute open treatment phase with citalopram. Three hundred twenty-seven patients who fulfilled the response criteria during the acute period (MADRS score ≤11) entered 16 weeks of continuation treatment. Individuals completing the continuation phase with an MADRS score ≤11 were randomized to receive double-blind treatment with citalopram or placebo (N=269). Recurrence was defined as an MADRS total score ≥22 or discontinuation due to the emergence of a new episode of depression during the double-blind period (as judged by three experts who did not participate in the study). Analysis of the evaluable patients (N=264) demonstrated recurrence rates of 18.2% (24/132) for the patients continuing on citalopram as compared with 44.7% (59/132) for patients switched to placebo (χ^2=24.4, *P*<.001). These findings, again, demonstrate that patients at risk for recurrence benefit from maintenance treatment.

Terra and Montgomery[23] reported the results of a long-term, double-blind, discontinuation trial of fluvoxamine. Two hundred four patients with MDD meeting criteria for remission (MADRS score <10 and a CGI-S score ≤2) by the end of an 18-week open-label phase were randomly assigned to fluvoxamine (100 mg/day) or placebo for 1 year. In this study, recurrence was defined as a reappearance of five or more *DSM-III-R* symptoms of depression or attempted suicide. During the 1-year double-blind period, 12.7% of fluvoxamine-treated patients had a recurrence of MDD, compared with 35.1% of placebo-treated patients (*P*<.001). The mean time to recurrence was 181 days for the fluvoxamine-treated group compared with 96 days for the placebo-treated group (*P*<.005). This study provides evidence that fluvoxamine is suitable for maintenance treatment by increasing the duration of time to recurrence or in some cases preventing recurrence of further episodes of depression within the first year.

These studies replicate and extend the work of Frank and colleagues,[20] demonstrating that maintenance treatment with any of a number of classes of antidepressant medication is more effective than placebo treatment in decreasing the risk of recurrence for patients with MDD. These findings strongly suggest that many patients with recurrent MDD should consider long-term, if not lifelong, maintenance treatment.

LIMITATIONS AND CONCLUSIONS OF THE CURRENT DATA

It is possible to draw some important global conclusions from the continuation and maintenance studies summarized in this article. Clearly, continuation antidepressant treatment decreases the rate of

relapse for patients with MDD who respond to acute antidepressant therapy. Furthermore, maintenance antidepressant therapy decreases the rate of recurrence of MDD. However, there are a number of important limitations to these data that need to be acknowledged.

First, these studies employ arbitrarily operationalized definitions of relapse and recurrence. Therefore, it is not possible to compare and contrast efficacy across studies of different antidepressant medications. Second, studies have different entry criteria, which again limits the ability to compare and contrast results across studies. Third, the patients included in these studies met specific types of inclusion and exclusion criteria that are valuable for research studies but may limit the generalizability of these data to usual clinical populations. A final but crucial limitation of these data is the fact that clinical trials themselves are artificial constructs employed as experimental surrogates for longitudinal naturalistic data. The structure of a clinical trial allows investigators to design relatively controlled experimental conditions that can be interpreted with inferential statistical analyses. Thus, empirical research investigates a relatively small cohort of convenience, employing arbitrary inclusion, exclusion, and outcome criteria, for only brief periods of time. These analyses are further complicated because the illness being studied is a syndrome rather than a specific disease. Factors such as the natural evolution of the syndrome and the importance of psychosocial stressors are ignored by the operationalized outcome criteria employed in these trials. Therefore, the results of these studies must be viewed cautiously and used appropriately to help each patient.

Recommendations for Continuation And Maintenance Treatment

There is a clear consensus that all patients with MDD require acute, continuation, and maintenance antidepressant treatment. There is agreement that the minimum length of treatment for an uncomplicated first episode of depression should be at least 9 months. However, if the first episode of depression is associated with any of the risk factors listed in the Table, the length of time for continuation and maintenance treatment should be increased. Unfortunately, the optimal length of therapy for these individuals is not known at this time.

Data from several publications generated by the NIMH-funded Collaborative Study of the Psychobiology of Depression demonstrate a number of disturbing findings. First, the majority of individuals identified in an index episode of MDD will have continued problems with minor depression, depressive symptoms, or recurrence of major depression when followed longitudinally.[24] Second, the vast majority of these

individuals (87%) will have another episode of major depression within the next 15 years.[18] Each episode of major depression seems to increase the risk of having additional episodes by as much as 15%.[25] Thus, for many individuals, MDD is a chronic condition with symptoms similar to those associated with hypertension. It is relatively well accepted that most individuals who have had three or more episodes of depression should be considered candidates for lifelong treatment with antidepressants. In addition, individuals who have had two episodes of depression should also be considered for continuous treatment if they have the risk factors described in the Table. More prospective data, such as those that will be generated by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study funded by the NIMH, will facilitate the development of more precise guidelines for continuation treatment of major depression.

Future Directions: Toward Remission

Future studies of MDD must include more investigations of factors that lead to acute and sustained remission rather than just symptomatic improvement. There are compelling data from a variety of sources suggesting that remission confers significantly superior outcomes. Judd and colleagues[24] demonstrated that patients who achieved complete remission of symptoms after an index episode of depression were less likely to have a recurrence of MDD. They also demonstrated in this analysis that achieving remission resulted in a fivefold increase in the length of time between episodes. Miller and colleagues[26] found that achieving remission had beneficial effects on psychosocial function among patients with chronic depression. In their analysis of a 12-week trial, they found a linear relationship between level of treatment response and Social Adjustment Scale–Self-Report (SAS-SR) scores. Patients who met criteria for remission had SAS-SR scores that were statistically indistinguishable from community normative values. These data are consistent with work by a variety of investigators, including Simon and colleagues.[27] They found that patients who were in remission missed fewer days at work, were more likely to maintain their employment, and had lower health care costs than patients who were partial responders or patients with treatment-resistant MDD. Thus, achieving remission is associated with a better clinical course and significantly better psychosocial functioning.

Unfortunately, there is a paucity of large, well-designed prospective studies that use a priori defined criteria for remission. Most of the data comparing and contrasting the remission rates for different antidepressant medications are either from post-hoc analyses of clinical trials,

mega-analyses, or meta-analyses. All of these techniques are powerful, but they have significant limitations. Post-hoc findings, such as the differences in remission rates observed in the Danish University Antidepressant Group comparative trials,[28,29] are valuable for hypotheses generation and sample-size determination. It is intriguing that the group of patients treated with the dual-action antidepressant clomipramine had more patients who met remission criteria than the citalopram-treated group. However, this is a secondary finding from a relatively small, acute study.

It is also true that there are published meta- and mega-analytic data suggesting that dual-action agents may be superior to single-action agents in achieving remission in acute treatment studies.[30,31] The limitations of such analyses must be clearly articulated. The selection of the number, design, and length of the trials included in such analyses can greatly alter the outcome. Furthermore, it is possible to use these techniques to identify findings that may be statistically significant yet represent small differences in effect sizes or even in clinical effects. Again, these data are best considered as important sources for generating hypotheses for future studies. Yet when viewed as a whole, these data suggest that large active comparator studies using a priori definitions of remission might add significantly to our understanding of potential differences between currently available antidepressant medications. Another benefit of such studies is that they may be used to identify clinical characteristics of patients who are more likely to achieve remission with antidepressant therapy.

Conclusion

MDD is a chronic, heterogeneous medical condition that requires long-term treatment for many patients. There is a growing body of evidence suggesting that achieving full remission early in the course of treatment helps protect against relapse and recurrence. Therefore, there must be a shift in the conceptualization of treatment success from the alleviation of symptoms toward the full resolution of MDD. In many instances, vigorous and continuous therapy is necessary to minimize the risk of further episodes of MDD. Research efforts designed to further our understanding of the benefits of long-term treatment are needed to ensure optimal patient care. ✤

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