Acute and Maintenance Treatment of Chronic Depression

David L. Dunner, M.D.

Chronic forms of depression account for approximately one third of all depressions. They are underrecognized and undertreated. This article defines the types of chronic depressions (dysthymic disorder, double depression, chronic major depression, and major depression in incomplete remission). A review of treatments for patients with these conditions is provided. The basic principles of treatment of chronic depression involve longer treatment and higher doses than are usually required for acute major depression. The impact of psychosocial disability and severity of depressive symptoms can be ameliorated with appropriate treatment. Newer treatments, such as the combination of psychotherapy and pharmacotherapy, may prove to be of greatest benefit for individuals with chronic mood disorders.

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The purpose of this article is to discuss the treatment of chronic depression. Chronic depression consists of mood disorders that persist for at least 2 years. The types of chronic depression defined in DSM-IV[1] include chronic major depressive disorder, dysthymic disorder, double depression, and major depressive disorder in incomplete remission[2] (Figure 1).

Chronic major depressive disorder usually has an onset in early to midlife, and the full syndrome of major depression persists for 2 years or longer. In some instances, patients who have experienced recurrent major depressive episodes can become chronically depressed. The course of the disorder is continuous moderate depression, but spontaneous remissions have been reported.[3]

Dysthymic disorder usually has an early onset. In fact, onsets after the age of 20 years are considered late. The full syndrome of a major depressive episode is not met for dysthymic disorder. Patients are described as having depressed mood and depressive symptoms "more days than not," but euthymic periods of up to 2 months can occur. Dysthymic disorder is differentiated from cyclothymic disorder in that there are "ups," or hypomanic periods, in cyclothymic disorder that do not exist in dysthymia. Dysthymic disorder is best viewed as a sporadic, persistent, and mild depression. The population frequency of this condition in epidemiologic data is around 3%.[4,5] However, for both chronic major depression and dysthymic disorder, there is significant psychosocial disruption.[6–8]

More than half of the patients with dysthymic disorder will develop a major depressive episode at some point in time after the onset of their dysthymia.[2,9] This combination has been termed *double depression* by Keller and Shapiro.[10] It is interesting that having a sporadic, mild, but chronic depression seems not to be sufficiently symptomatic to cause patients with dysthymia to present specifically for treatment of their mood disorder or be recognized by their primary care physician as having depression. They are more likely to present when their depression worsens and develops into a major depressive episode.

The fourth group of people with chronic major depression consists of individuals who have a major depressive episode at the onset of their illness but who only partially recover, and the lack of complete remission persists for at least a 2-year period. These individuals, who may have recurrent major depressive episodes, are poorly studied. Research has not firmly established the frequency of this condition.

Chronic depression in one form or another accounts for about a third of all depression.[2] Chronic depression is more psychosocially disabling than acute major depression.[6–8] High rates of comorbid Axis I and II disorders are frequently seen, and it is likely that individuals with chronic depression develop characteristics of "depressive personality disorder," including self-blame, beliefs of inadequacy, low self-esteem, and worthlessness.[1] Recent studies[11] clearly show the benefit of long-term treatment of recurrent major depression, and studies[12–14] also indicate the benefit of long-term treatment for the chronic depressions.

From the Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle.

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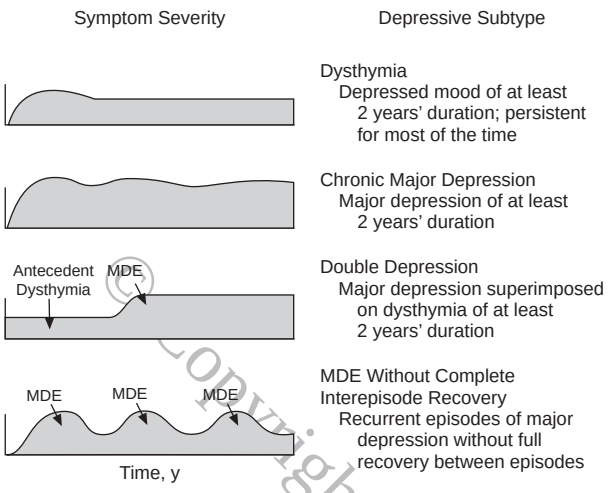
Reprint requests to: David L. Dunner, M.D., Department of Psychiatry and Behavioral Sciences, University of Washington, 4225 Roosevelt Way NE, Suite 306-C, Seattle, WA 98105-6099 (e-mail: ddunner@u.washington.edu).

Figure 1. Clinical Presentations of Chronic Depression[a]



[a]Adapted in part from Keller et al.[2] Chronic depression reflects a mood state of 2 years or longer. Abbreviation: MDE = major depressive episode (as defined in the DSM system).

The principles of treatment of the chronic depressions involve the following: first, the newer medications have greater tolerability as compared with tricyclic antidepressants for the treatment of depressive states, and in particular of mild depressive states.[15,16] Thus, the newer drugs are preferable because of greater tolerability. Second, all treatments for depression are likely to be effective for the chronic depressions including dysthymic disorder, but only fluoxetine, sertraline, venlafaxine, mirtazapine, and bupropion have been studied for dysthymic patients and, of the newer agents, sertraline and nefazodone for chronic depression.[12–14,17–25] However, longer treatment and higher doses are required for the chronic depressions than for acute major depression. Finally, the role and efficacy of psychotherapy in these conditions are poorly studied, and the available data support the need for a greater number of psychotherapy sessions for individuals with chronic as compared with acute depression.[26–28]

DYSTHYMIC DISORDER

Several studies[12,17–25,29] report efficacy of antidepressant agents for the treatment of dysthymic disorder. One of the difficulties with these studies is the lack of large patient samples at individual sites. Thus, single sites are more likely to be reported as open-label trials or very small placebo-controlled trials. A large multicenter study of fluoxetine versus placebo has been reported by Vanelle et al.,[18] and a multicenter study of sertraline, imipramine, and placebo has been reported by Thase et al.[20] Both of these studies showed that long-term treatment is important and that high doses of medications are also important. For the Thase et al.[20] study, 17 sites enrolled a total of 416 patients who had primary early-onset dysthymia. These patients were studied over a 12-week period and were randomly assigned to treatment with sertraline, imipramine, or placebo. Both active treatments showed benefit over placebo. The dropout rate with imipramine treatment was significantly higher than that with sertraline, demonstrating the lower tolerability of tricyclic antidepressants for mild depressive states. The mean dose at the end of the trial was approximately 200 mg/day for imipramine and about 140 mg/day for sertraline (relatively high doses). These data support at least a 3-month treatment with pharmacotherapy for dysthymic disorder.

My colleagues and I[19] conducted a randomized trial of cognitive-behavioral therapy and fluoxetine in dysthymic patients. This was a 16-week trial, and 31 subjects entered. The subjects were randomly assigned to treatment with blind assessment at weeks 8 and 16. The dose of fluoxetine was fixed at 20 mg/day. Findings from this study indicate that both treatments were effective and were not significantly different from each other in terms of outcome. The longer patients were in treatment, the greater the percentage of responders, i.e., there was a greater number of responders at 16 weeks than at 8 weeks for each treatment. The small sample size may have impacted our ability to demonstrate significant differences between treatments, since there seemed to be some advantage for fluoxetine over cognitive-behavioral therapy at the end of 16 weeks in terms of remission rates among completers.

Bupropion sustained release (SR) has been studied in a recent trial by Hellerstein et al.[25] This was an open-label study of 16 dysthymic subjects who were treated for 8 weeks. Response was defined as a 50% or greater decrease in the Hamilton Rating Scale for Depression (HAM-D) score from baseline and a Clinical Global Impressions-Improvement scale score of 1 or 2 (very much or much improved). Seventy-five percent of these subjects were responders. The mean dose was 365 mg/day.

At the Center for Anxiety and Depression at the University of Washington, my colleagues and I[19,21,22] have undertaken other studies of dysthymic patients. These studies showed positive results from small numbers of subjects treated on an open-label basis with venlafaxine[21] and with mirtazapine.[22] Our early studies focused on treating individuals with low doses of antidepressants. Our rationale was that dysthymia is a mild depression and low doses might be quite effective. However, in a placebo-controlled fluvoxamine trial (D.L.D.; H. E. Hendrickson, M.D.; C. Bea, unpublished data), 2 of the fluvoxamine-treated patients developed major depressive episodes toward the end of the study, and 2 of the placebo-treated patients became euthymic toward the end of the study. The mean dose of fluvoxamine in that study was about 100 mg/day (a low dose). The DSM-IV definition of dysthymic disorder includes up to 2-month euthymic periods. Also, as has been noted, many dysthymic patients may develop major de-

pressive episodes.[2,9] The results from our fluvoxamine-placebo study showed a drug-placebo difference favoring placebo. We concluded that single-site studies with small groups of subjects were probably useful only to pilot the way for larger controlled trials. We also concluded that a higher dose of fluvoxamine was preferable to a lower dose. On the basis of findings from the fluvoxamine study, we reviewed the duration of euthymia in dysthymic patients. We found that the duration of euthymia in dysthymic patients prior to treatment ranged from 2 to 30 days, with a mean of about 8 days.[30] Thus, the tendency of dysthymic patients to have symptom-free intervals clearly presents a confound in the design of studies with small numbers of subjects, since subjects may continue to be dysthymic yet appear symptom-free at an index rating session.

Psychotherapy trials in dysthymic patients, in addition to the one noted above, include a study of group cognitive therapy and sertraline in dysthymic outpatients. Reductions in mean HAM-D ratings were not significantly different for the group that received both treatments and the group that received only sertraline.[23] Markowitz[26] also reported on a small number of subjects who responded to interpersonal psychotherapy. Dysthymic patients respond to cognitive-behavioral psychotherapy, although a lower response rate in dysthymic patients is usually found for the 16 to 20 sessions generally needed for acute depression.[19,27,28]

Thus, the management guidelines for treatment of dysthymic patients include the use of high doses of medication. The rationale for this is the tendency for some patients to develop major depressive episodes, which can occur during the course of treatment. Secondly, long treatment trials, probably on the order of 12 weeks, are needed in order to show efficacy as contrasted with the 6-week treatment trial that is commonly used for acute major depression. The rationale for this is the likelihood that personality effects of having a chronic disorder are not likely to change quickly.

Criteria for determining recovery from dysthymia have been proposed, but further research in this area is probably necessary.[31] The duration of treatment for this condition is clearly not established on a research basis. The recommendations are to provide treatment for a year and to strive for complete remission of symptoms rather than just an improvement in symptoms. Psychotherapy alone has been poorly studied, and extra sessions may be required to obtain remission.[19,27,28] Research combining sertraline and group psychotherapy[23] has not shown that combined treatment enhances efficacy compared with sertraline alone.

CHRONIC MAJOR DEPRESSION

For most treatment studies of chronic depression, individuals with chronic major depression, double depression with a current major depressive episode, and recurrent major depressive disorder in incomplete remission with a current major depressive episode are usually grouped together. The placebo response rate in such trials is generally lower than that reported in studies of acute major depression.[32–37] Similarly, the treatment response rates are also lower than those usually seen for acute major depression.[31–44] Studies of acute major depression generally show about a 50% to 60% response rate at 6 weeks of treatment. Studies of chronic depression generally show about a 50% response rate at 12 weeks of treatment.

Table 1. Relapse Rates With Drug Versus Placebo in Continuation Studies

Drug/Study	Weeks of Treatment	Relapse With Drug, %	Relapse With Placebo, %	p Value
Fluoxetine[45]	52	26	57	p < .01
Paroxetine[46]	52	16	43	p < .001
Sertraline[47]	44	13	46	p < .001
Citalopram[48]	24	11	31	p < .05
Mirtazapine[49]	20	4	23	p < .05
Nefazodone[50]	36	17	33	p < .0001

Studies of antidepressants have provided data regarding continuation treatment (the "continuation phase" is a 4- to 12-month period after acute treatment response). These studies are generally designed such that patients who respond to an acute treatment phase of 6 weeks or longer are randomly assigned to continue treatment with the drug at the dose to which they responded or be switched to placebo. Continuation studies persist for up to about a year. All of the reports thus far clearly support the notion that continued treatment shows a better response than switching to placebo[45–50] (Table 1). However, it is of interest that continued treatment does not show a perfect response rate and that a variable but significant percentage of patients will relapse or have a recurrence of depression in spite of continuation treatment at the dose and drug with which they improved during acute treatment.

Kocsis et al.[43] studied imipramine versus placebo treatment for 6 weeks in patients with chronic depression. Subjects who had a history of dysthymic disorder were included, and 96% of the 76 patients actually had a current major depressive episode at the time of entry to the study. Only 4% met criteria for dysthymia alone. Fifty-eight percent of the patients met DSM-III criteria for chronic major depression (met criteria for major depressive episode for at least 2 years prior to entry into the study). The results of this study showed that 59% of the imipramine-treated patients and 13% of the placebo-treated patients met response criteria (6 points or less on the 24-item HAM-D, a 10-point or greater improvement on the Global Assessment of Functioning scale, and absence of sufficient symptoms to meet diagnostic criteria for dysthymia). This was a statistically significant difference. Considering an intent-to-treat population, 45% of imipramine-treated and 12% of placebo-treated patients were considered respond-

ers (also statistically significantly different). The mean dose of imipramine was 198 mg/day. There was a higher dropout rate for imipramine-treated patients than for placebo-treated patients.

A subsequent trial by the Kocsis group[29] compared desipramine treatment in 42 patients who had double depression and 33 patients who had pure dysthymia. This was an 8-week open-label trial using a mean dose of 220 mg/day. Full response was defined as a score of 6 or less on the 24-item HAM-D. Partial response was defined as at least a 50% reduction from the baseline HAM-D score, with a final score between 7 and 12. Fifty-two percent of patients with current major depression showed a partial or complete response, and 71% of patients with pure dysthymia showed a partial or complete response. This result was not statistically different.

Kocsis et al.[44] also reported on 51 patients with pure dysthymia, 64 patients with double depression, and 14 patients with chronic major depression. These patients were treated with desipramine on an open-label basis for 10 weeks. Remission was defined as a score of 7 or less on the 24-item HAM-D and a Global Assessment of Functioning rating greater than 70 on 3 consecutive biweekly ratings. Partial response was defined as at least a 50% reduction from the baseline HAM-D score, with a final score between 7 and 12, and a Global Assessment of Functioning score of 60 or greater on 3 successive ratings. A continuation phase for responders followed and lasted for an additional 16 weeks. Patients who were considered partial responders or remitters to the continuation phase were then randomly assigned to continue desipramine or be tapered to placebo and were followed for a 2-year period. Relapse rates during the maintenance phase were 52% for the placebo group and 11% for the desipramine group. This difference was statistically significant. The mean dose during the acute phase was 227 mg/day. During the continuation phase, 50 patients did not change status, 3 full remitters became partial responders, 7 partial responders became remitters, and 1 partial responder relapsed. These data indicate that long-term treatment at high antidepressant doses is important and that continued treatment enhances the response rate.

Two very large studies of chronic depression were recently undertaken. The first was a 635-patient multicenter trial involving 12 sites.[13] The study involved treatment through an acute treatment phase with sertraline or imipramine, a crossover treatment for those who failed to respond to their initial acute treatment assignments, a continuation phase for 4 months for full and partial responders to the acute and crossover phases, and then a maintenance phase for continuation phase responders for slightly longer than a year. Patients who responded continued on treatment with the medication to which they responded at the dose that was needed for their response. During the maintenance phase, sertraline-treated patients were randomly assigned to continue sertraline or be switched to placebo. The mean final dose of sertraline for the acute phase was about 140 mg/day and for imipramine, about 200 mg/day. Dropout rates significantly favored sertraline over imipramine. Full remission was defined as a Clinical Global Impressions-Improvement scale score of 1 or 2 (very much or much improved) and a 24-item HAM-D score of 7 or less. Partial response involved the same Clinical Global Impressions-Improvement scale score, 15 points or less on the HAM-D, and a Clinical Global Impressions-Severity of Illness scale score of 3 or less (mildly ill). Both drugs showed equal efficacy, with a slightly better than 50% response rate for the acute phase. Partial responders to the acute and crossover phases tended to continue to improve, and full responders tended to maintain their response during the continuation phase. The maintenance phase data showed a statistically significant separation for sertraline compared with placebo. These data suggest that the chronic depressions of the types entered into this trial (chronic major depression, double depression with a presenting major depressive episode, and recurrent depression in incomplete remission with an acute major depressive presenting episode) should be treated for at least a 2-year period once antidepressant response is achieved.

The second study of treatment of chronic forms of depression[14] was designed to assess the role of psychotherapy in the treatment of chronic depression. A sluggish response of patients with chronic depression to cognitive-behavioral therapy has been noted.[19,28] In order to enhance response to psychotherapy, a new psychotherapy, Cognitive Behavioral Analysis System of Psychotherapy (CBASP), was developed and specifically designed for the treatment of chronically depressed patients.[51] Prior to involvement in the treatment study, psychotherapists were certified in use of CBASP, and their therapy was supervised for adherence to treatment principles throughout the clinical trial.

Nefazodone was selected as the medication for this trial because long-term pharmacotherapy might be enhanced if the medication lacks long-term side effects. Long-term antidepressant side effects that are particularly troublesome to patients include weight gain and sexual dysfunction. These side effects may be problematic with long-term treatment with selective serotonin reuptake inhibitors and at times result in discontinuation of treatment in patients who are otherwise doing well. Weight gain and sexual side effects are uncommon with nefazodone treatment.

The study involved random assignment of chronically depressed patients to CBASP monotherapy, nefazodone monotherapy, or combination therapy. An acute 12-week treatment phase was conducted, and nonresponders to monotherapy were crossed over to the other therapy. For the acute treatment phase, remission was defined as 8 points or less on the 24-item HAM-D at both weeks 10 and 12. Partial response was defined as a 50% decrease in the 24-item HAM-D score from baseline, with the total score

Table 2. Rates of Response and Remission From the Acute Phase of the Nefazodone/Cognitive Behavioral Analysis System of Psychotherapy (CBASP) Chronic Depression Study[a]

Group	CBASP, % (N = 173)	Nefazodone, % (N = 167)	Nefazodone + CBASP, % (N = 179)
Completers			
Remission	24	22	42
Significant response	28	33	43
Total response	52	55	85
Modified intent-to-treat sample			
Total response rate	48	48	73

[a]Data from Keller et al.[14] For the comparison of combined nefazodone and CBASP with nefazodone, $p < .0001$; for the comparison of combined nefazodone and CBASP with CBASP, $p < .0001$; for the comparison of nefazodone with CBASP, the p value was not significant.

between 9 and 15. Complete and partial responders to the acute and crossover phase were continued for a 4-month continuation phase on the therapy to which they responded, and then a maintenance phase ensued involving randomization of nefazodone-treated patients to continue nefazodone or be switched to placebo and randomization of CBASP patients to continue monthly CBASP or have monthly clinic visits.

The data from the acute phase of this study have been analyzed and are available.[14] The acute phase data suggest that monotherapy (CBASP or nefazodone) produced about 50% response rates, whereas combined therapy produced an 85% response rate (Table 2). This is indeed the first time that combined psychotherapy and pharmacotherapy was shown to be of greater benefit than monotherapy alone for the treatment of depression.

The mean daily dose of nefazodone used in this trial was about 500 mg and did not differ significantly among the groups. The rates of discontinuation were similar in the 3 treatment groups with approximately 24% of all patients not completing the 12-week acute phase. Discontinuation due to lack of efficacy was low (1%) in each group. The adverse event dropout rate was 14% in the nefazodone monotherapy group and, interestingly, 7% in the combined therapy group and 1% in the CBASP monotherapy group. The most common reason for dropout in the CBASP monotherapy group was withdrawal of consent, at 14%, perhaps due to the need to visit the clinic twice a week during the first 6 weeks for treatment. The findings from the acute phase regarding sexual dysfunction clearly indicated that there was no significant increase in treatment-emergent sexual dysfunction comparing the nefazodone-treated groups with the psychotherapy-alone group.[52] There was no significant increase in weight over the acute and continuation phases for the nefazodone-treated group as compared with the CBASP-only group.

Psychosocial outcome also improved, more so in the combined treatment group than in the monotherapy groups.[53] Responders showed an improvement in psychosocial functioning as compared with nonresponders. Pharmacoeconomic analysis of the data showed that although treatment costs were highest with combined therapy and lowest with nefazodone monotherapy, cost offsets due to increased productivity made the cost savings with combined therapy nearly equal to that seen with nefazodone monotherapy.[54]

Data from the crossover phase suggested that individuals who were treated initially with nefazodone, but who did not respond, responded better to a subsequent trial of CBASP than individuals who were nonresponders to initial treatment with CBASP and who subsequently were treated with nefazodone. Reasons for this interesting crossover effect are not clear.

The continuation phase data showed positive results for maintaining and improving response. Overall response was maintained in 80% of the CBASP monotherapy group, 82% of the nefazodone monotherapy group, and 90% of the combination therapy group. In addition, individuals who entered the continuation phase as responders but who still had residual symptoms (i.e., partial responders) tended to improve, and remission was achieved in 46% of the CBASP group, 52% of the nefazodone group, and 53% of the combined therapy group by the end of the continuation phase. Individuals who were in complete remission at entry of the continuation phase tended to maintain their response status equally across all 3 treatment groups. In summary, a high rate of response was maintained in the continuation phase with additional improvement in those who entered with residual symptoms.

SUMMARY

Chronic depression is a frequent form of mood disorder. Individuals with the chronic forms of depression tend to have greater psychosocial disability and work impairment than individuals with acute major depression. Treatment principles for improving patients with chronic forms of depression involve longer treatment at higher doses than are used for acute major depression, whether the treatment involves a psychotherapy (more sessions) or a pharmacotherapy (higher doses).

Several questions regarding treatment of these conditions remain. Regarding dysthymia, the efficacy of combined psychotherapy and pharmacotherapy has not yet been shown to be of an interactive benefit. How long to continue treatment for patients with dysthymia is also unclear.

Two recent studies of chronic depression[13,14] provide an excellent source of information regarding the need for long-term treatment in these subjects. The role of psychotherapies, CBASP in particular, in the treatment of chronic depression may provide a very meaningful approach to enhance treatment outcome. The selection of medication for individuals who will require long-term treatment should

take into account long-term issues such as acute and long-term tolerability, since it is likely these medications will need to be continued for considerable periods of time.

The sequencing of psychotherapy in the treatment plan may also prove to be an important strategy. Should one begin with medication and in nonresponders or partial responders apply psychotherapy, or should one preferentially apply combined treatment at the onset, or perhaps even psychotherapy first?

These issues are likely to be decided by further definitive research projects. However, it is very clear that the research effort in defining and improving treatment for chronic depression has resulted in solid evidence leading to rational selection of available treatments for the clinician to apply.

Drug names: bupropion (Wellbutrin), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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