New Strategies for Treating Chronic Depression

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This article provides an update on the diagnosis of chronic depression subtypes, the clinical and public health significance of chronic depression, and a review of what is known about its treatment. The efficacy of antidepressant medications for pure dysthymia and double depression has been established, yet fewer than 50% of patients have achieved full remission with a single agent. Traditional antidepressant psychotherapies appear to have limited effectiveness for chronic depression. In one recent study, a combination of cognitive behavioral analysis system of psychotherapy and a newer antidepressant, nefazodone, yielded the highest response and remission rates ever reported in this population (73% response rate, 48% remission rate in an intent-to-treat sample). This combination merits further study for treatment of chronic depression. *(J Clin Psychiatry 2000;61[suppl 11]:42–45)*

CLINICAL AND PUBLIC HEALTH SIGNIFICANCE OF CHRONIC DEPRESSION

Depressive disorders have traditionally been conceptualized as episodic, remitting conditions. However, over the past 2 decades it has become apparent that many, if not most, depressed patients have a chronic course, with long periods of full-syndromal and residual symptomatology.[1,2] As many as 50% of patients with major depressive disorder (MDD) either have a preexisting history of dysthymia (i.e., double-depression)[3,4] or exhibit a pattern of recurrent episodes with significant interepisode symptomatology (chronic MDD).[4]

Chronic depression is a significant public health problem. Recent epidemiologic studies indicate that 3% to 6% of persons in the community have chronic depression.[5,6] Chronic depressions are associated with high rates of psychosocial and work impairment[7,8] and health care utilization.[6,9] In addition, persons with chronic depression exhibit significantly greater functional impairment[10,11] and more frequent suicide attempts and hospitalizations[12] than outpatients with acute MDD. Owing to their frequent early onset[13] and often lifelong course, chronic depressions probably account for a substantial portion of the enormous direct and indirect costs associated with depression.[14] Development of newer medications with better tolerability for long-term treatment and novel psychotherapy approaches that may be more specific for chronic depression have recently set the stage for improved treatment of chronic forms of depression.

DIAGNOSTIC CONSIDERATIONS

Four major forms of chronic depression have been discussed in the recent literature: (1) dysthymia, (2) double depression, (3) chronic MDD, and (4) recurrent MDD with incomplete recovery between episodes. Dysthymia sometimes presents in a "pure" form, but more frequently presents with a superimposed major depressive episode. This has been referred to as "double depression."[15] Over 75% of patients with dysthymia experience superimposed major depressive episodes at some point in their lives,[4] and approximately 25% of patients presenting with MDD have a preexisting dysthymia.[15] Chronic MDD refers to a major depressive episode that has persisted for at least 2 years. Prospective longitudinal studies indicate that approximately 20% of patients presenting with an acute MDD have not recovered after 2 years,[16] and 12% have not recovered after 5 years.[17] The DSM-IV criteria for chronic MDD are more restrictive than the DSM-III-R criteria in that they require that full criteria for MDD are met continuously for at least 2 years, whereas DSM-III-R required that the episode last 2 years without a period of 2 months or longer with no significant depressive symptoms. As a result of this change, some of the patients who were classified as having chronic MDD in DSM-III-R are now classified as having recurrent MDD, without full interepisode recovery, with no antecedent dysthymic disorder. Approximately 20% of patients with MDD exhibit a pattern of recurrent episodes with significant residual symptomatology between recurrences.[4]

"Pure" dysthymia (i.e., without a superimposed major depressive episode) differs from the 3 chronic forms of MDD in that it is milder and exhibits a higher

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placebo response rate.[18] In contrast, double depression and DSM-III-R chronic MDD (which includes both DSM-IV chronic MDD and many cases of recurrent major depression with incomplete remission between episodes) are similar with respect to demographic and clinical characteristics, family history, and response to antidepressant medication.[19]

PHARMACOTHERAPY OF CHRONIC DEPRESSION

The efficacy of antidepressant medications has been established for the short-term treatment of pure dysthymia and double-depression[18,20–29] by placebo-controlled randomized clinical trials (RCTs). Drugs found to be superior to placebo for chronic depression have included tricyclic antidepressants,[18,27,28] serotonin reuptake inhibitors,[18,22,25,28] and other agents (e.g., moclobemide,[27] amisulpride,[23,24,26] amineptine,[24] ritanserin[20,21]). These studies have ranged in duration from 6 to 12 weeks and have yielded intention-to-treat response rates (typically defined as a 50% or greater reduction in Hamilton Rating Scale for Depression [HAM-D] score) in the range of 45% to 55%. Because roughly 40% of the responders do not meet criteria for full remission, only 25% to 35% of those randomized actually end up fully recovered after an acute phase of treatment. Chronic major depression has not yet been studied in placebo-controlled RCTs. Three studies have compared treatment of chronic major and double depression with 4 different antidepressants and have found comparable rates of response for these 2 diagnostic subtypes.[30–32]

Thus far, only a single study has addressed the treatment of chronically depressed nonresponders to an initial antidepressant trial. Thase et al.[33] reported on patients with either double or chronic depression. Nonresponders to 12 weeks of treatment with sertraline or imipramine were then crossed over to the opposite drug for an ensuing 12-week period. Sixty percent of those crossed over to sertraline and 44% of those crossed over to imipramine were categorized as responders.

Continuation therapy, i.e., continued treatment of responders for the purpose of prevention of relapse of chronic depression, has been examined in 2 studies[30,34] that continued active drug for 4 months. These studies reported outcomes separately for patients who entered continuation as full or partial remitters. Fully remitted patients generally remained in remission and experienced low relapse rates during continuation therapy with desipramine, sertraline, or imipramine. Substantial proportions (30%–40%) of patients entering as partial responders in these studies ended continuation as full remitters, thus suggesting the value of longer term treatment for chronically depressed patients with partial response in acute treatment.

Maintenance therapy for chronic depression has recently been addressed as well. Kocsis et al.[30] randomly assigned chronically depressed patients who had remained in remission during continuation therapy with desipramine to receive continued desipramine or be tapered to placebo. Over a 2-year maintenance-treatment phase, relapse rates were 52% for the placebo group and 11% for the desipramine group. Keller et al.,[35] in a maintenance-phase efficacy study of sertraline for chronic depression, reported that sertraline afforded significantly greater prophylaxis against recurrence or reemergence of depressive symptoms than did placebo.

Although the RCTs reviewed above have established the efficacy of antidepressants for acute and maintenance treatment of chronic depression, important gaps remain in our ability to treat these conditions. The major shortcoming is the limited proportion of responders and fully remitted patients following treatment with any single agent. This leaves open for further study the value of sequential algorithms of treatment, the value of augmentation strategies for patients who are not fully responsive, and the potential value of antidepressant psychotherapy as an alternative or adjunctive treatment.

PSYCHOTHERAPY OF CHRONIC DEPRESSION

Several authors[36,37] have reviewed the literature on targeted psychotherapies of chronic depressions. Most of the extant studies have been open rather than controlled trials, and almost all have sought to assess the efficacy of psychotherapy as a monotherapy, rather than an adjunctive treatment, for dysthymic disorder or chronic major depression. Most studies were compromised by small sample size and other methodological limitations.

Cognitive-behavioral therapy (CBT) has been found to have measurable but modest effects in treating dysthymic disorder or chronic major depression, with a mean response of about 31%.[38] Interpersonal psychotherapy (IPT) had been reported to be potentially helpful in an open trial comprising only a handful of patients.[39] Although a larger trial of IPT as a primary treatment for dysthymic disorder is underway and another has been completed,[40] no definitive results are yet available as to its efficacy.

The literature on combination treatment of chronic depression using pharmacotherapy and psychotherapy is still more meager. In an open trial, Miller et al.[41] found that 2 of 4 treatment-refractory inpatients with DSM-III double depression responded to the combination of either CBT or social skills training (SST) and assorted psychotropic medications (antidepressants as well as neuroleptics in 2 cases).

Becker et al.[42] reported preliminary results on 39 mildly symptomatic dysthymic subjects randomly assigned to either SST or crisis-supportive psychotherapy and to nortriptyline or placebo. Patients received 16 weekly psychotherapy sessions followed by 2 sessions every 2 weeks. Initial 17-item HAM-D mean score was 10.9, declining to 4.5 at termination. Self-report and clinician ratings showed significant improvement for all 4 treatment conditions. Waring et al.[43] described preliminary results in 12 women

meeting research diagnostic criteria for dysthymia [sic] randomly assigned to 10 weeks of cognitive marital or supportive therapy and to doxepin (maximum dose = 150 mg/day) or atropine placebo. All patients improved (mean HAM-D score pretreatment = 14.5, posttreatment = 7.1). Final results have never been reported for either the Becker et al. or the Waring et al. study.

Ravindran et al.[44] treated patients who had pure dysthymic disorder with 12 weeks of sertraline in doses up to 200 mg/day (mean ± SD = 178 ± 29 mg/day), or placebo. In each group, half were randomly assigned to receive 12 sessions of adjunctive "cognitive-behavioral" group psychotherapy. Sertraline, with or without group therapy, significantly reduced depressive symptoms. Effects of group therapy alone were not significantly greater than the placebo condition. Some methodological issues raised by this study bear emphasis: (1) patients were diagnosed with dysthymia, not chronic major depression; (2) its sample size limited statistical power to show differences; and (3) a previously untested group psychotherapy intervention was used, rather than a targeted individual psychotherapy.

These studies indicate the limits of the historical literature in this area. All patients who received combination treatment did so from the outset of treatment. None of these studies addressed the benefit of a targeted antidepressant psychotherapy as adjunctive treatment for patients who had not fully responded to a pharmacotherapy trial. The small sample sizes in these studies precluded statistical power to determine treatment differences. Most of the studies involved "pure" dysthymic disorder rather than other forms of chronic depression.

COMBINING ANTIDEPRESSANT MEDICATION AND PSYCHOTHERAPY FOR CHRONIC DEPRESSION—A NEW APPROACH

Understanding the limitations of the available treatments, a consortium of academic investigators approached a pharmaceutical company and received support for a large multisite collaborative study[32] that examined the value of a combination of a new antidepressant—nefazodone and a new antidepressant psychotherapy—cognitive behavioral analysis system of psychotherapy (CBASP)—developed by McCullough[45] and specifically targeted to chronic depression.

The study compared the combination with nefazodone (maximum dose = 600 mg/day) alone and with CBASP (16–20 sessions) alone over a 12-week period. Six hundred sixty-two patients with chronic MDD, MDD plus dysthymic disorder (double-depression), or recurrent MDD with incomplete interepisode recovery were randomized to 1 of the 3 treatments. Results are summarized in Table 1. The combination treatment proved to be significantly more effective than either monotherapy. HAM-D scores were reduced more by the combination. Overall response rates were 48% for CBASP, 48% for nefazodone, and 73% for the combination (intention-to-treat sample). Among completers, the respective response rates were 52%, 55%, and 85%, respectively. Overall attrition rates were similar in each treatment group. Secondary analyses revealed that monotherapy with nefazodone had superior effects on symptom reduction over CBASP during the first 6 weeks of treatment and that nefazodone alone or in combination with CBASP improved sleep more than CBASP. The results of this study were impressive and important because combined treatment was found to be more beneficial than either monotherapy and because this combination yielded the highest response and remission rates ever reported in this population.

Table 1. Response and Remission Rates for Patients Treated With Nefazodone, Cognitive Behavioral Analysis System of Psychotherapy (CBASP), or Their Combination[a]

Variable	Nefazodone (A)	CBASP (B)	Nefazodone + CBASP (C)	p Values A vs B	A vs C	B vs C
Completer sample, N	167	173	179			
Total response	92 (55)	90 (52)	152 (85)	.57	.0001	.0001
Remission	36 (22)	41 (24)	75 (42)	.64	.0001	.0003
Satisfactory response	56 (34)	49 (28)	77 (43)	.30	.07	.004
Nonresponse	73 (44)	83 (48)	27 (15)	...	...	...
Intent-to-treat sample, N	220	216	226			
Total response	105 (48)	103 (48)	165 (73)	.99	.0001	.0001
Remission	65 (30)	72 (33)	109 (48)	.39	.0001	.0015
Satisfactory response	40 (18)	31 (14)	56 (25)	.28	.09	.0059
Nonresponse	113 (51)	113 (52)	57 (25)	...	...	...

[a]Data from Keller et al.[32] All values shown as N (%) unless specified otherwise. For the completer sample, 2 patients in the nefazodone group completed the study but response could not be determined owing to absence of week 10 or week 12 24-item Hamilton Rating Scale for Depression (HAM-D-24) scores. For the intent-to-treat sample, there was no post-randomization HAM-D-24 score obtained for 6 patients (2 in nefazodone and 4 in combined treatment groups). Remission was defined as a HAM-D-24 score ≤ 8 at both weeks 10 and 12 (completers) or exit (intent-to-treat). Satisfactory response was defined in the completer sample as a ≥ 50% reduction in HAM-D score from baseline at both weeks 10 and 12, and HAM-D score ≤ 15 at both weeks 10 and 12, but > 8 at either week 10 or 12. For the intent-to-treat sample, the definition was the same except exit values were employed.

SUMMARY

This article has updated readers on the diagnosis and clinical significance of chronic depression and reviewed treatment studies conducted in the past 15 years. Emphasis has been given to gaps in clinical knowledge and research methods. An important new approach to treatment of chronic depression employed a combination of a newer antidepressant medication (nefazodone) and a putative chronic depression–specific psychotherapy (CBASP). Results indicated that this combination yielded substantially

higher rates of response than either nefazodone or CBASP alone. Further studies will be required to explore longer term response to medication and psychotherapy, to investigate alternative and adjunctive treatments for nonresponding patients, and to determine if differential response to medications and/or psychotherapy can be predicted by clinical characteristics in chronically depressed patients.

Drug names: atropine (Donnatal and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), nefazodone (Serzone), sertraline (Zoloft).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, these agents are not approved by the U.S. Food and Drug Administration for dysthymic disorder: atropine, doxepin, and sertraline.

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