CME Activity

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CME Objectives
After completing this CME activity, the reader will:

- Have a better awareness of the concept of refractory depression (i.e., what the clinician should do before defining an episode of depression as treatment refractory)
- Know current cognitive-behavioral strategies that may be applied when pharmacologic treatments fail
- Be aware of the central role of anxiety disturbances and subclinical symptoms in depression

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Cognitive-Behavioral Management of Drug-Resistant Major Depressive Disorder

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Background: The application of cognitive-behavioral treatment to drug-resistant major depression has received little research attention.

Method: Nineteen patients who failed to respond to at least two trials of antidepressant drugs of adequate dosages and duration were treated by cognitive-behavioral methods in an open trial.

Results: Three patients dropped out of treatment. The remaining 16 patients displayed a significant ($p < .001$) decrease in scores on the Clinical Interview for Depression after therapy. Twelve patients were judged to be in remission at the end of the trial; only 1 of these patients was found to have relapsed at a 2-year follow-up. Antidepressant drugs were discontinued in 8 of the 12 patients who responded to cognitive-behavioral treatment.

Conclusion: These preliminary results suggest that a trial of cognitive-behavioral therapy by an experienced therapist should be performed before labeling an episode of major depression as "refractory" or "treatment resistant." These latter terms should apply only when a psychotherapeutic effort has been made. Until then, it seems more appropriate to define depression as "drug refractory" or "drug treatment resistant."

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The problem of treatment resistance in depression is attracting increasing attention. Several pharmacologic strategies have been developed for depressed patients who fail to respond to standard drug treatment.[1,2] Limited research has been done on nonpharmacologic approaches, despite the logical appeal of treating patients who do not respond to antidepressant medication with psychotherapy.[2] Such appeal is increased by the emerging role of cognitive-behavioral strategies in mood disorders[3] and by the recent awareness that these strategies may improve residual symptoms that persist despite successful antidepressant drug therapy.[4,5]

A few studies are, however, available. Fennell and Teasdale[6] failed to detect a significant effect of cognitive therapy on five chronic, drug-refractory depressed outpatients. Antonuccio et al.[7] applied a psychoeducational group treatment (including relaxation, increasing pleasant activities, cognitive strategies, and social skills) to 10 outpatients with unipolar depression who had not responded to antidepressant medication. All patients continued drug treatment. One dropped out of group treatment, 4 were no longer depressed, 2 showed some improvement, and 3 were still depressed after psychoeducational group treatment. Improvements were maintained at a 9-month follow-up.[7] Miller et al.[8] examined the effectiveness of a treatment program consisting of cognitive-behavioral treatment, pharmacotherapy, and short-term hospitalization in six chronic, drug-resistant depressed females. The approach produced a substantial improvement in the majority of patients. De Jong et al.[9] studied a group of 30 chronically depressed patients who failed to respond to antidepressant drugs. Patients were randomly assigned to an intensive inpatient cognitive-behavioral program, to an inpatient low-intensity milieu therapy, and to a waiting list control group. Patients treated with the intensive cognitive-behavioral program had the better outcome. Cole et al.[10] treated 16 inpatients who had refractory major depression with cognitive therapy and found a remission rate of 69%, with a significant decrease in depression rat-

ings. Thase and Howland[11] reported a remission of 47% in 17 patients with major depression resistant to antidepressant treatment after participation in an inpatient cognitive-behavioral program. The aim of our study was to test the effectiveness of cognitive-behavioral treatment in a carefully selected group of depressed patients who had failed to respond to at least two courses of adequate drug treatment.

METHOD

Subjects

Twenty consecutive depressed outpatients satisfying the criteria below, who had been referred to the Affective Disorders Program of the University of Bologna School of Medicine, were enrolled in the study. The patients' diagnoses were established by the consensus of a psychiatrist (G.A.F.) and a clinical psychologist (C.R.) independently using the Schedule for Affective Disorders and Schizophrenia (SADS).[12] Subjects had to meet a current diagnosis of major depressive disorder according to Research Diagnostic Criteria (RDC),[13] and have no history of manic, hypomanic, or cyclothymic features or active drug or alcohol abuse or dependence. Treatment resistance was defined as persistence of RDC major depressive disorder despite at least two courses of adequate drug treatment. Adequate drug treatment was defined as use of standard doses of antidepressant drugs (i.e., significantly superior to placebo in double-blind studies) administered continuously for a minimum duration of 6 weeks.[1] Further, as suggested by Simpson and Kessel,[14] one trial should include the use of a high-dose (200–300 mg) tertiary amine such as imipramine for a minimum of 6 weeks. The failed treatment was provided for the current episode of depression.

Patients were carefully screened for medical illnesses that could be responsible for the depressive symptoms and their response.[15] In one case, a large non-secreting pituitary adenoma was found, and depression abated after neurosurgical intervention. The remaining 19 patients had a mean ± SD age of 41.2 ± 10.9 years. There were 6 men and 13 women. Ten patients were married and 9 were single. The majority of patients (N = 14) belonged to the middle-upper social class[16] and had had more than 13 years of education (N = 11). The mean ± SD duration of illness was 20.8 ± 14.6 months. Depression was primary according to RDC in 11 cases and secondary in the remaining 8 cases. Six patients were at their first depressive episode, whereas 13 had had more. In 10 of the 19 cases, major depression was superimposed on dysthymia, and "double depression"[17] was thus found to occur. The 19 patients had been treated with the following antidepressant drugs: imipramine (10 cases), amitriptyline (10 cases), fluoxetine (6 cases), desipramine (5 cases), clomipramine (4 cases), and mianserin (3 cases). Seven patients had also undergone long-term (longer than a year) psychodynamic therapy unsuccessfully.

Assessment

The 19 patients were assessed by a clinical psychologist (S.G.) who did not take part in the treatment. She administered the change version of Paykel's Clinical Interview for Depression (CID),[18] encompassing 20 items, each rated on a 1- to 7-point scale. This is a shortened version of the full 36-item scale that was found to be extremely sensitive in detecting change in treatment outcome.[18,19] It covers a wider range of symptoms compared to other scales[20] and is particularly suitable for assessing subclinical symptomatology of affective disorders.[4,5,20–24] It does offer, therefore, considerable advantages compared to other more commonly used scales, such as the Hamilton Rating Scale for Depression, in assessing residual symptomatology and incomplete recovery.[25] Further, it has been fully and independently validated for Italian populations.[21,22,26–28] The CID-Change Version[18] has a total score that ranges from 20 (minimum) to 140 (maximum). Ten items (depressed feelings, guilt, pessimism, suicidal tendencies, impaired work and interests, anorexia, delayed insomnia, retardation, agitation, and depressed appearance) can be extracted to characterize a depression score that excludes other, less specific, affective disturbances, such as anxiety and irritability.

Treatment Procedures

Informed consent was secured from all subjects. Patients were then assigned to cognitive-behavioral treatment according to a protocol described in detail below. Treatment should consist of at least ten 40-minute sessions once every other week. Three patients dropped out of treatment. The mean number of sessions was 15 ± 4 for the remaining 16 patients. At the beginning of cognitive-behavioral therapy, antidepressant drugs were tapered at the rate of 25 mg of amitriptyline or its equivalent every other week. Tapering was stopped if it resulted in symptom exacerbation. All psychotherapies were conducted by two experienced therapists (G.A.F., G.S.), who also handled the pharmacologic management of patients. Both therapists had more than 10 years of experience in cognitive-behavioral treatment of depression. Seven patients had undergone long-term (longer than a year) psychody-

namic therapy in the past. The patients were reassessed with the CID after treatment by the same clinical psychologist who had performed the previous evaluations. They were also rated according to Kellner's global rating of improvement.[29] Only the patients rated as "better" or "much better" according to this scale and showing at least a 50% reduction in the CID depression score were judged as responders. The patients were then assessed 3, 6, 12, 18, and 24 months after treatment. Follow-up evaluations consisted of a brief update of clinical and medical status, including any treatment contacts or use of medications. Relapse was defined as the occurrence of an RDC-defined episode of major depression.

Treatment Protocol

Substantial modifications on the classical treatment protocol by Beck et al.[30] were performed as the result of clinical experience in cognitive-behavioral treatment of residual symptoms of depression.[4] Such modifications were not in the specific behavioral and cognitive techniques that were employed (such as activity scheduling, mastery and pleasure tasks, graded exposure, and identifying and modifying automatic thoughts and dysfunctional beliefs) but in their focus, sequencing, and planning. First, treatment was directed to anxiety symptoms as much as depressive symptoms. There was considerable emphasis on exposure strategies related to anxiety,[31] as well as on anxiety-provoking automatic thoughts.[32] Second, patients' disturbances were conceptualized in terms of inhibited central pleasure-reward mechanisms (e.g., low self-esteem, pessimism), central pain disturbance (e.g., sadness, anxiety, excessive regard for potentially adverse consequences of actions), and psychomotor regulation (e.g., exhaustion, slowing of thoughts), according to Carroll's model.[33] Treatment sequence mainly involved behavioral techniques for inhibited psychomotor regulation and anxiety in central pain disturbance in the first phase of treatment, and cognitive strategies for mood and inhibited central pleasure-reward mechanisms in the second part of treatment. In both cases (activities homework and automatic thoughts monitoring), structured diaries were used.

Statistical Methods

A paired, two-tailed, Student's t test was used to evaluate differences in CID scores before and after treatment.

RESULTS

Twelve (63%) of the 19 patients who began treatment met criteria for response. Among the nonresponders, 3 dropped out within the first five sessions. These patients (2 women and 1 man) showed poor compliance with homework assignments (e.g., diary) and displayed poor cooperation. In two cases, major depression was superimposed on long-standing dysthymia.

Pretreatment and posttreatment CID scores were available for the 16 completers. The total score of the CID decreased from 54.1 ± 9.0 to 31.4 ± 8.4 after cognitive-behavioral treatment of depression ($t = 6.52$, $df = 15$, $p < .001$). Half of the 12 patients who were judged to be responders had no residual symptoms according to specific criteria.[4] Only 1 of the 12 responders relapsed at a 2-year follow-up. No therapist effects were detected.

Despite the small sample size and thus the preliminary nature of our results, several interesting, even though preliminary, factors were associated with response. Double depression was present in 5 (71%) of the 7 patients who failed to display response and in 5 (42%) of the 12 who recovered. Discontinuation of antidepressant drugs was achieved in 1 of the 7 patients who did not respond to cognitive-behavioral therapy and in 8 of the 12 who responded. The patient who relapsed was drug-free. Three of the 7 patients who did not respond and 4 of the 12 who did had undergone previous dynamic psychotherapy.

DISCUSSION

This study has obvious limitations because of its preliminary nature. First, it was an open clinical trial. The positive results that were obtained could be largely nonspecific and due to the self-recovering characteristics of depressive illness. Second, it had a naturalistic design: patients underwent a variety of pharmacologic therapies. Finally, cognitive-behavioral treatment was provided by two very experienced therapists. The results might have been different with less experienced therapists. Nonetheless, the study provides new, important clinical insights regarding the treatment of unipolar major depressive disorder.

Cognitive-behavioral treatment was found to be effective in the majority of patients who had been refractory to drug treatment. Further, only 1 of the 12 patients who were judged to be in clinical remission had relapsed at a 2-year follow-up, despite discontinuation of drug treatment in the majority of patients. The results were clinically impressive in view of several factors. First, relatively strict criteria for defining drug-resistant depression, including at least one trial with tricyclic antidepressants at high doses for an adequate time,[14] were used. Second, patients had a long mean duration of current major depres-

sive illness (20.8 months), and there were 10 cases of double depression. Finally, since all of the patients had no response to at least two courses of antidepressant pharmacotherapy, they would be expected to have a low rate of response attributable to attention-placebo factors. The fact that a number had no response to long courses of prior (dynamic) psychotherapy would mitigate against a favorable response to nonspecific aspects of psychotherapeutic support. The design of the study did not allow us to discriminate whether the therapeutic results were the consequence of a joint use of pharmacologic and psychotherapeutic strategies, or whether drug treatment was a redundant ingredient. The available literature would suggest that when either behavior therapy, cognitive therapy, or interpersonal psychotherapy is combined with antidepressant treatment, the effects usually do not differ significantly from either treatment used alone.[3]

In 4 of the 12 patients who responded, however, tapering of antidepressant drugs resulted in symptom exacerbation, which suggested retaining pharmacotherapeutic treatment. Cognitive-behavioral treatment and drug therapy may be similarly effective on certain depressive symptoms.[3] The effects they do not share, however, may be important in determining a differential sensitivity to treatment of specific patients. There is increasing evidence[34,35] that psychotherapy may have a favorable impact on multiple neurotransmitter systems. It is conceivable, therefore, that changes in norepinephrine and dopamine pathways (central pleasure-reward mechanisms), in serotonin and acetylcholine balance (central pain disturbance), and in dopamine and acetylcholine balance (psychomotor regulation)[33] may occur as a result of cognitive-behavioral modification. The degree of neurotransmitter involvement by cognitive-behavioral therapy may, thus, be larger than with single pharmacotherapeutic tools and may parallel that entailed by augmentation strategies in drug treatment of refractory depression. The type of cognitive-behavioral strategies that were used in this study was likely to maximize these neurobiological activations.

It has been frequently reported that cognitive-behavioral management of refractory depression requires modifications from the standard strategies. Cole et al.[10] emphasized the importance of brief but frequent (20 minutes, three times a week) initial sessions as well as of incorporating techniques developed in cognitive therapy of personality disorders. Thase and Howland[11] suggested the need of frequent sessions to enhance learning and retention, of homework assignments and in-session rehearsal, and of involvement of spouse or significant others to provide psychoeducation. Our cognitive-behavioral protocol departed from standard cognitive strategies. In the initial phase of therapy, it was characterized by refraining from cognitive techniques while using behavioral modification particularly as to psychomotor regulation. Anxiety was regarded as a target of treatment as much as was depression. Exposure therapy was therefore used extensively.[31] Specific cognitive ingredients were introduced only at a later stage. We feel that treatment of anxiety is often insufficiently emphasized during cognitive therapy of depression, probably since anxiety is regarded as a by-product of depression. However, as discussed in detail elsewhere,[25,36] at least in certain types of depression, anxiety and irritability are the key symptoms, while mood lowering is a subsidiary phenomenon. Accordingly, anxiety and irritability are prominent in the prodromal phase of depression,[21,36] may be covered by mood disturbances but are still present in its acute phase,[37] and are again a prominent feature of its residual phase.[4] A considerable degree of cooperation is required by the patient (homework). Not surprisingly, the 3 patients who dropped out displayed considerable compliance problems with cognitive-behavioral treatment. Lack of congruence between patients' and therapists' expectations of potential treatment interventions[38] might be another factor associated with dropout.

Overlap between the concepts of refractory depression and depression with residual symptomatology is considerable.[25] The response to antidepressant treatment is often subsumed under a categorical rubric (present/absent). Yet, in most cases, it lies in between: the degree of residual symptomatology that is regarded as appropriate is a function of the assumptions of the clinician, the thoroughness of posttreatment psychopathologic investigation, and the patient's satisfaction.[25] As a result, there are close links between cognitive-behavioral management of residual symptomatology in depression[4,39] and psychotherapeutic treatment of refractory depression. This should lead one to consider current protocols of cognitive treatment of depression as amenable to considerable improvement. Reliance on orthodoxy—an ever present danger of all psychotherapeutic movements—seems to prevail instead.

The findings of this study lend support to the previous investigations on cognitive-behavioral management of refractory depression.[7–11] They challenge the frequent use of unspecified terms such as "refractory depression" or "treatment-resistant depression." A trial of cognitive-behavioral treatment by an experienced therapist appears to be a reasonable option for patients who failed to respond to drug treatment and may yield substantial ben-

efits in at least half of patients. The terms "refractory" or "treatment resistant" should apply only when a psychotherapeutic effort has also been made. Until then, it seems more appropriate to define depression as "drug refractory" or "drug treatment resistant." Similarly, it would be inappropriate to label as refractory a major depressive episode that failed to respond to cognitive-behavioral therapy, but was not given the chance of adequate drug treatment.[40]

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others).

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Cognitive-Behavioral Management of Drug-Resistant Major Depressive Disorder

1. A major depressive disorder can be defined as refractory when it does not respond to:
   a. A single course of standard doses of antidepressant drugs
   b. Two separate trials of antidepressant drugs at adequate dosages
   c. An extended course of cognitive behavioral treatment
   d. Both pharmacotherapy (two trials) and cognitive behavioral psychotherapy
   e. None of the above
2. The effects of cognitive behavioral treatment in depression are:
   a. Increased by concurrent pharmacotherapy
   b. Decreased by concurrent pharmacotherapy
   c. Decreased in drug-refractory depression
   d. Increased in drug-refractory depression
   e. None of the above
3. Anxiety is important in major depressive disorders because:
   a. It is present in the prodromal phase
   b. It is present in the residual phase
   c. Symptoms are often partially affected by pharmacotherapy
   d. It is part of the central pain disturbance
   e. All of the above

Circle the one correct answer for each question.

1.	a	b	c	d	e
2.	a	b	c	d	e
3.	a	b	c	d	e

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   - C. Enabled the reader to become aware of the central role of anxiety disturbances and subclinical symptoms in depression ____
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