Cognitive Behavior Approach to Loss of Clinical Effect During Long-Term Antidepressant Treatment: A Pilot Study

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Objective: The aims of this investigation were to explore the feasibility of a cognitive behavior approach to loss of clinical effect during long-term antidepressant therapy and to compare it with dose increase.

Method: Ten patients with recurrent depression who relapsed while taking antidepressant drugs were randomly assigned to dose increase and clinical management or to cognitive behavior therapy and maintenance of the antidepressant drug at the same dose.

Results: Four of five patients responded to a larger dose, but all had relapsed again on that dose by the 1-year follow-up. Four of five patients responded to cognitive behavior therapy, and only one relapsed during follow-up.

Conclusions: The data suggest that application of a cognitive behavior therapy approach is feasible when there is a loss of clinical effects during long-term antidepressant treatment and may carry long-term benefits. The results need to be confirmed with large-scale controlled studies.

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The return of depressive symptoms during maintenance antidepressant treatment is a common and vexing phenomenon. It was found to occur in 9%–57% of patients in published trials (1). A number of pharmacological strategies have been suggested for addressing loss of antidepressant efficacy (increase or decrease in dose, drug augmentation, or switching to a different drug).

In a large multicenter controlled trial involving fluoxetine (2), dose increase for relapse during maintenance treatment of major depression was found to be effective in the majority of patients. The literature, however, suggests flat dose-response curves for many antidepressant drugs (1). Nonpharmacological strategies have not been tested, to our knowledge. In recent years, cognitive behavior strategies have emerged as a tool for sustaining and improving remission in recurrent depression (3).

The aims of this pilot investigation were to assess the feasibility of a cognitive behavior approach to relapse during maintenance treatment of recurrent major depression and to compare its effectiveness with that of a dose increase.

Method

Ten consecutive outpatients satisfying the criteria, who had been referred to and treated in the Affective Disorders Program of the University of Bologna in Italy, were enrolled in the study. The patients' diagnoses were established by the consensus of two psychiatrists (G.A.F. and C. Rafanelli) independently using the Schedule for Affective Disorders and Schizophrenia (4). Subjects had to meet the following criteria: 1) a relapse of major depressive disorder according to the Research Diagnostic Criteria (RDC) (5) while receiving long-term antidepressant therapy (longer than 6 months); 2) relapse should not have been caused by compliance problems; 3) treatment had been initiated when the patient was in his or her third or greater episode of depression, with the immediately preceding episode being no more than 2.5 years before the onset of the current episode (6); 4) no history of manic, hypomanic, or cyclothymic features; 5) no history of active drug or alcohol abuse or dependence or of personality disorders, according to DSM-IV criteria; 6) no history of antecedent dysthymia; 7) no active medical illness; and 8) successful response to antidepressant drugs administered by a psychiatrist. The 10 patients were treated with the following antidepressant drugs: 20 mg/day of fluoxetine (three patients), 15 mg/day of mirtazapine (three patients), 100 mg/day of amitriptyline (two patients), 50 mg/day of fluvoxamine (one patient), and 100 mg/day of desipramine (one patient). The mean duration of treatment was 9 months (SD=2). The mean number of depressive episodes was 4.3 (SD=1.3). Comorbidity consisted of generalized anxiety disorder (two patients), social phobia (one patient), and agoraphobia (one patient). There were four men and six women. The mean age was 44.3 years (SD=11.1). Written informed consent was secured from all patients. No patient declined to participate or dropped out of treatment.

All patients were assessed by a clinical psychologist (C. Ruini), who was blind to treatment assignment for all the duration of the study. She administered the change version of Paykel's Clinical Interview for Depression (7), encompassing 20 items, each rated on a 1–7-point scale. This scale is particularly sensitive in detecting change in treatment outcome and is suitable for detecting subclinical symptoms of affective disorders (7–9). The patients were randomly assigned to one of two treatment groups: 1) dose increase of antidepressant drug (50% increase with tricyclics and doubling of dose with the other antidepressants) and clinical management or 2) maintenance with the same dose of antidepressant and the addition of cognitive behavior therapy. Both treatments were administered by the same psychiatrist (G.A.F.), and therapy consisted of six 30-minute sessions, once every week. Clinical management consisted of reviewing the patient's clinical status and providing the patient with support and advice, if necessary (8). Cognitive behavior therapy consisted of use of cognitive restructuring for distorted views and maladaptive beliefs, exposure for phobic symptoms, lifestyle modification, and well-being therapy (8, 9). After 6 weeks, the patients were assessed again with the Clinical Interview for Depression by the same clinical psychologist, who was blind to treatment assignment. They

were also rated according to Kellner's global rating of improvement (10). Only the patients rated as "better" or "much better" according to this scale and showing at least a 50% reduction in score on the Clinical Interview for Depression were judged to be responders. The patients were then assessed 3, 6, 9, and 12 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.

Results

Four of five patients responded to dose increase and clinical management. All four patients, however, relapsed while receiving the higher dose during the 12-month follow-up (two within 3 months, one between 3 and 6 months, and one between 9 and 12 months).

Four of five patients responded to cognitive behavior therapy and medication at the same dose. Only one of the four relapsed during follow-up (between 9 and 12 months).

Discussion

The study has obvious limitations because of its preliminary nature. First, it involved a very small number of patients. Second, it had a seminaturalistic design, since patients were treated with different types of antidepressant drugs. Finally, treatment was provided by only one psychiatrist, who has extensive experience in affective disorders and cognitive behavior therapy. Nonetheless, the study provides new, important clinical insights regarding management of loss of clinical effect during treatment with antidepressant drugs in recurrent depression.

The application of a modified sequential form of cognitive behavior therapy (8, 9) was found to be feasible for addressing loss of antidepressant efficacy and to be as effective as dose increase and clinical management. However, although a new relapse occurred for all patients receiving a higher medication dose, this occurred in only one of the four patients treated with cognitive behavior therapy. These results need to be confirmed by large-scale investigations. However, they are in line with both the frequent occurrence of a second relapse after an increase in dose during maintenance treatment (2) and the literature on the relapse-preventing effects of cognitive behavior therapy in depression (3, 8, 9). Loss of the placebo effect is an unlikely explanation for relapse since only patients who had been in remission for at least 6 months after the initiation of antidepressants were included.

These findings point to a novel use of cognitive behavior therapy in depression, in addition to those previously established, such as treatment of a depressive episode, relapse prevention, and treatment of drug-refractory depression (3): restoring and maintaining remission with antidepressant drugs when response fails or is about to fail.

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