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

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Background: The return of depressive symptoms during maintenance antidepressant treatment is a common phenomenon, but has attracted very limited research attention. The aims of this investigation were to explore the feasibility of a family intervention approach to loss of clinical effect during long-term antidepressant therapy and to compare this approach with dose increase.

Method: Twenty outpatients with recurrent major depressive disorder (diagnosed using Research Diagnostic Criteria, i.e., patients were at their third or greater episode of major depressive disorder, with the immediately preceding episode being no more than 2.5 years before the onset of the episode which led to antidepressant treatment) who lived with a partner and relapsed while taking antidepressant drugs were randomly assigned to (1) family intervention approach according to the McMaster Model and maintenance of the antidepressant drug at the same dosage or (2) dose increase and clinical management. A 1-year follow-up was performed. The study was conducted from January 2002 to December 2004.

Results: Seven of 10 patients responded to an increased dosage; all but 1 relapsed again on that dosage during follow-up. Seven of 10 patients responded to family intervention, but only 1 relapsed during follow-up. The difference in relapse was significant ($p < .05$).

Conclusions: The data suggest that application of a family intervention approach is feasible when there is a loss of clinical effect during long-term antidepressant treatment, and this approach may carry long-term benefits. The results need to be confirmed by large-scale controlled studies but should alert the physician to explore the psychosocial correlates of loss of clinical effect.

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The return of depressive symptoms during maintenance antidepressant treatment is a common and vexing phenomenon.[1] It was found to occur in 9% to 57% of patients in published trials.[2]

The recent STAR*D study data[3,4] provide a dramatic exemplification of the extent of the problem. Among the patients who achieved remission and who were encouraged to continue the previously effective acute treatment medication, rates of relapse ascended with each treatment step, ranging from 33.5% at level 1 to 50% at level 4. When the cumulative remission rate of 67% after 4 treatments was corrected for relapse rate, it decreased to 43%.[4] A number of pharmacologic strategies have been suggested for addressing loss of antidepressant efficacy (e.g., increase or decrease in dose, augmentation, and/or change to a different drug). In a large multicenter controlled trial involving fluoxetine,[5] drug increase for relapse during maintenance treatment of major depressive disorder was found to be effective in the majority of patients. The literature, however, suggests flat dose-response curves for many antidepressant drugs.[2]

Cognitive-behavioral strategies have emerged as a tool for sustaining and improving remission in recurrent major depressive disorder.[6] In a small pilot investigation, 10 patients with recurrent major depressive disorder who relapsed while taking antidepressant drugs were randomly assigned to dose increase and clinical management or to cognitive-behavioral therapy supplemented by well-being therapy and maintenance of the antidepressant drug at the same dose.[7] Four of 5 patients responded to a larger dose, but all had relapsed again on that dose by the 1-year

follow-up. Four of 5 patients responded to the cognitive-behavioral approach, and only 1 relapsed during follow-up. A case report[8] successfully applied a family intervention approach based on the McMaster Model[9] to loss of clinical effect during antidepressant treatment.

The aim of this pilot investigation was to compare the effectiveness of a family intervention for loss of clinical effect during maintenance treatment of recurrent major depressive disorder with the effectiveness of dose increase in patients living with a partner.

METHOD

Twenty consecutive outpatients satisfying the criteria described below, who had been referred to and treated in the Affective Disorder Program of the University of Bologna in Italy, were enrolled in the study, which was conducted from January 2002 to December 2004. The patients' diagnoses were established by the consensus of 2 psychiatrists (G.A.F and C.R.), independently using the Schedule for Affective Disorders and Schizophrenia.[10]

Subjects had to meet the following criteria: (1) a relapse of major depressive disorder according to Research Diagnostic Criteria,[11] while taking long-term antidepressant therapy (longer than 6 months); (2) relapse should have not been caused by compliance problems; (3) treatment was initiated when patients were at their third or greater episode of major depressive disorder, with the immediately preceding episode being no more than 2.5 years before the onset of the episode[12]; (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; (8) successful response to antidepressant drugs administered by a psychiatrist; and (9) the patient was living with a partner.

Prior to the admission in the trial, the 20 patients were treated with the following antidepressant drugs: amitriptyline 100 mg/day (2 cases); citalopram 20 mg/day (1 case); clomipramine 100 mg/day (1 case); desipramine 100 mg/day (3 cases); fluoxetine 20 mg/day (4 cases); fluvoxamine 100 mg/day (2 cases); mirtazapine 15 mg/day (2 cases), 30 mg/day (4 cases); paroxetine 20 mg/day (1 case). Mean duration of antidepressant treatment was 9.7 (SD = 2.6) months. Mean number of depressive episodes was 3.7 (SD = 1.1). Comorbidity (assessed after antidepressant treatment) consisted of obsessive-compulsive disorder (1 case), hypochondriasis (1 case), and agoraphobia (1 case). There were 8 men and 12 women. Mean age was 46.7 (SD = 8.2) years. Written informed consent was secured from all patients and partners who participated in the study after the procedures were explained to them. No one declined to participate.

At baseline and after treatment (12 weeks), all patients were assessed by a clinical psychologist (E.T.), who was blind as to treatment assignment for the entire duration of the study. She administered the change version of Paykel's Clinical Interview for Depression (CID),[13] encompassing 20 items, each rated on a 1 to 7 point scale. This scale is particularly sensitive in detecting change in treatment outcome, and it is suitable for detecting subclinical symptomatology of affective disorders.[13–16] Patients were randomly assigned to 1 of 2 treatment conditions: (1) maintenance with the same dosage of antidepressants and addition of family intervention or (2) dose increase of antidepressant drugs (50% increase with tricyclics and doubling the dose with the other antidepressants) and clinical management.

The family intervention, defined as Problem Centered Systems Therapy of the Family, is based on the family conceptualization provided by the McMaster Model.[7] The Problem Centered Systems Therapy of the Family is articulated in 4 main macro stages: (1) assessment, (2) contracting, (3) treatment, and (4) closure. The treatment is based upon the following basic principles: emphasis on macro stages of treatment (especially assessment); collaborative set; open and direct communication with the family (paradoxical interventions are not allowed); emphasis on current problems; focus on behavioral changes; focus on family strengths; and time limitations (6 to 12 sessions). Once the family problems are identified, the treatment goal is to allow the family to develop problem-solving abilities in order to solve the identified problems. Treatment intervention is geared toward producing behavioral and cognitive changes. Family members are asked to practice identifying and dealing with problems in life, and the therapist can model effective ways of problem solving. Tasks are behavioral and concrete enough that they can be easily evaluated; they are also oriented toward increasing positive behaviors rather than decreasing negative ones. Emotionally oriented tasks emphasize positive feelings rather than negative ones. Our protocol included 6 sessions, lasting 1 hour each, every other week.

Clinical management consisted of reviewing the patient's clinical status and providing the patient with support and advice if necessary.[14] It consisted of six 30-minute sessions, 1 every other week. Family intervention was performed by a clinical psychologist trained in the McMaster Model (S.F.). Clinical management was performed by the treating psychiatrist (G.A.F.). After treatment, the patients were assessed again with the CID by the same clinical psychologist, who was blind as to treatment assignment. They were also rated according to Kellner's global rating of improvement.[17] Only the patients rated as "better" or "much better" according to this scale and showing at least a 50% reduction in the CID score were judged as 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

Table 1. Sociodemographic Data, Clinical Characteristics, and Treatment Responses of the 2 Groups of Patients With Recurrent Major Depressive Disorder (N = 20)

Variable	Dose Increase + Clinical Management (N = 10)	Dose Maintenance + Family Therapy (N = 10)	Significance
Age, mean (SD), y	46.0 (9.1)	47.5 (7.7)	NS[a]
Sex: men/women	4/6	4/6	NS[b]
Social class: lower/upper	4/6	4/6	NS[b]
Education: lower/upper	6/4	5/5	NS[b]
No. of previous depressive episodes, mean (SD)	4 (1.3)	3.4 (0.7)	NS[a]
Drug treatment duration prior to inclusion in the study, mean (SD), mo	9.4 (2.4)	10.0 (2.7)	NS[a]
CID baseline score, mean (SD)	59.9 (4.8)	51.3 (5.6)	$p < .01$[a]
CID posttreatment score, mean (SD)	35.4 (14.9)	26.0 (11.3)	NS[c]
Treatment response: yes/no	7/3	7/3	NS[b]
Relapse: yes/no	6/1	1/6	$p < .05$[b]

[a]By t test.
[b]By Fisher exact test.
[c]By analysis of covariance.
Abbreviations: CID = Clinical Interview for Depression, NS = not significant.

medical status, including any treatment contacts or use of medications. Relapse was defined as the occurrence of a Research Diagnostic Criteria–defined major depressive episode and was determined by blind rater.

The 2-tailed t test and Fisher exact probability test were used to evaluate differences between the 2 groups and changes after treatment. Analysis of covariance was used for comparing the CID scores after treatment, with adjustments for any differences in the first assessment. Intent-to-treat analysis was performed. Further, logistic regression was performed.

RESULTS

There were no significant differences in sociodemographic characteristics between the 2 groups (Table 1). The mean number of depressive episodes and drug treatment duration prior to the inclusion in the study were not significantly different (Table 1). At baseline, the severity of depression as assessed by CID total scores was significantly higher ($t = 3.7$, $df = 18$, $p < .01$) in the dose-increase group compared to the other group (Table 1).

When the posttreatment CID scores were compared in the 2 groups, using initial measurements as covariates, there were no significant differences between the groups (Table 1).

Seven of 10 patients responded to an increased dosage; all but 1 relapsed again on that dosage during follow-up. Seven of the 10 patients responded to family intervention, but only 1 relapsed during follow-up (Table 1). The difference was significant.

In order to verify whether the higher relapse rate was an effect of the higher CID scores reported at baseline and not just an effect of treatment condition, we performed a logistic regression. The analysis showed that the initial CID scores had no significant effect on the likelihood of relapse, whereas such effect was provided by treatment condition ($p = .019$, odds ratio = 36.00, 95% CI = 1.80 to 718.68).

DISCUSSION

The study has obvious limitations due to its preliminary nature. First, it involved a small number of patients. Second, it had a seminaturalistic design, since patients were treated with different types of antidepressant drugs, and the time dedicated to each patient was unbalanced between the 2 groups (patients who underwent family interventions were given more time compared to clinical management). Third, only in the case of family treatment were partners involved (they participated in all treatment sessions), whereas in the case of clinical management, partners were not involved in treatment. Fourth, the results pertain only to patients living with a partner. Finally, the inclusion criteria were quite restrictive (no compliance problems, drug abuse, personality disorder, or medical illness).

Nonetheless, the study provides new, important clinical insight regarding management of loss of clinical effect during treatment with antidepressant drugs in recurrent major depressive disorder. The application of family intervention was found to be feasible for addressing loss of antidepressant efficacy and, in the short term, to be as effective as dose increase and clinical management. In the long term, the data clearly show that the chances of relapse were significantly higher in the dose-increase group. While a new relapse ensued in 6 of the 7 patients who responded to an increase in the medication regimen, relapse occurred only in 1 of the 7 patients who were successfully treated with the family intervention during a 1-year follow-up.

The results need to be confirmed by large scale investigations. However, they are in line with the frequent occurrence of a second relapse after increasing dosage during maintenance treatment,[5] with the relapse-preventing

effects of psychotherapy in depression,[14] and with the controlled trials of marital therapy in depressed patients.[9,18–21] Loss of placebo effect is an unlikely explanation for relapse since only patients who kept remission for at least 6 months after initiation of antidepressant were included.

The findings illustrate the importance of psychosocial factors, such as life events affecting the family balance,[22] in influencing relapse during maintenance treatment. Even though a systematic assessment of the occurrence of life events was not performed in this study, in many instances patient relapse was associated with the occurrence of a specific life event, such as retirement, couple difficulties, problems with the extended family, and a daughter deciding to leave home.

The results may thus alert the physician who observes a loss of clinical effect during long-term antidepressant treatment to explore the psychosocial setting of such loss and, according to the patient's difficulties, refer him/her to individual cognitive-behavioral therapy[7] or family intervention.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil and others).

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