Course of Depressive Symptoms Over Follow-up

Findings From the National Institute of Mental Health Treatment of Depression Collaborative Research Program

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• We studied the course of depressive symptoms during an 18-month naturalistic follow-up period for outpatients with Major Depressive Disorder treated in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. The treatment phase consisted of 16 weeks of randomly assigned treatment with the following: cognitive behavior therapy, interpersonal therapy, imipramine hydrochloride plus clinical management (CM), or placebo plus CM. Follow-up assessments were conducted at 6, 12, and 18 months after treatment. Of all patients entering treatment and having follow-up data, the percent who recovered (8 weeks of minimal or no symptoms following the end of treatment) and remained well during follow-up (no Major Depressive Disorder relapse) did not differ significantly among the four treatments: 30% (14/46) for those in the cognitive behavior therapy group, 26% (14/53) for those in the interpersonal therapy group, 19% (9/48) for those in the imipramine plus CM group, and 20% (10/51) for those in the placebo plus CM group. Among patients who had recovered, rates of Major Depressive Disorder relapse were 36% (8/22) for those in the cognitive behavior therapy group, 33% (7/21) for those in the interpersonal therapy group, 50% (9/18) for those in the imipramine plus CM group, and 33% (5/15) for those in the placebo plus CM group. The major finding of this study is that 16 weeks of these specific forms of treatment is insufficient for most patients to achieve full recovery and lasting remission. Future research should be directed at improving success rates of initial and maintenance treatments for depression.

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Numerous studies have investigated the efficacy of standardized, short-term psychotherapeutic treatments for outpatient, nonbipolar depression.[1] The most well known of these treatment approaches include cognitive behavior therapy (CBT),[2] interpersonal therapy (IPT),[3] and a variety of behavioral treatment approaches.[4-7] Efficacy has been reported for these treatments by findings of no differences or superior outcome compared with standard antidepressant medication conditions or superior outcome compared with a variety of control conditions. The National Institute of Mental Health Treatment of Depression Collaborative Research Program (TDCRP), a multisite collaborative study, investigated the efficacy of CBT and IPT in comparison with a standard reference condition of imipramine hydrochloride plus clinical management (CM) and pill placebo plus CM for the treatment of outpatients with Major Depressive Disorder (MDD).[8] Outcome findings for depressive symptoms and general functioning at termination of treatment have been reported.[9] Very briefly, in the treatment phase no significant differences were found between either of the psychotherapies and imipramine plus CM at termination from treatment; however, imipramine plus CM showed an advantage in its more rapid effects.[10] Short-term results also provided some evidence for the efficacy of IPT compared with placebo plus CM in terms of recovery, although the findings for IPT were less consistent than for imipramine plus CM. For those patients who were more severely depressed and functionally impaired at pretreatment, there was some evidence of the efficacy of IPT and strong evidence of the efficacy of imipramine plus CM. With regard to CBT, although patients improved nearly as much as the patients who underwent IPT, there was an absence of sig-

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nificant differences in outcome between CBT and the placebo plus CM condition.

An important question regarding the effectiveness of psychotherapy concerns its ability to effect more lasting change, especially given the high rates of relapse and recurrence of depression.[11,12] That is, do the techniques and strategies of the short-term psychotherapeutic approaches for depression do what they are designed to do: help patients develop more adaptive coping mechanisms and enable them to deal more effectively with their lives and with the symptoms of depression? If they do, then such lasting effects of the psychotherapies might be evidenced in the delay of relapse, in the attenuation of the severity or duration of future episodes of depression, or in the prevention of relapse altogether. Earlier studies have attempted to address this question. Follow-up studies of short-term treatment with CBT have reported better posttreatment outcome for patients responding to CBT compared with patients responding to an antidepressant.[13-17] Patients treated with IPT have been found to have better social functioning, but not less depression, at 1 year follow-up.[18]

The purpose of this article is to report findings from the TDRCP on the posttreatment course of patients during an 18-month naturalistic follow-up period. This long-term follow-up of short-term results provides an estimate of the enduring quality of the remission induced by the various treatments. This is of considerable value, as it indicates the likelihood that patients recovering following a particular kind of treatment will become depressed again during the period of time defined by the follow-up period. However, *comparisons* of treatment conditions for relapse rates after recovery do not yield immediately interpretable causal inferences about "enduring effects," since the patient groups defined by recovery on different treatments may have different latent relapse tendencies. For example, a completely inactive placebo would select for natural remission, which might be "enduring," while a highly potent treatment might select additionally for patients who remain well only when they are treated. Thus, after treatment discontinuation, the relapse rate would be lower in the placebo group, purely from selection.

Aside from the question of "causality," the long-term follow-up of the TDCRP provides clinically useful data as discussed above. First, we extend the examination of the short-term outcomes of the treatments to the longer term. The comparison of the long-term outcome of the treatment groups of the entire original sample (ie, the proportion who recover in the short-term phase and remain well following treatment termination) has implications for the choice of initial treatment strategies.

Second we present data that bear on a clinically relevant question: given that one recovers in a given treatment condition, what is the probability of relapse? We also examine other subsequent outcomes, including receiving treatment for depression and amount of time without symptoms of depression. Finally, we use these results to generate hypotheses about "enduring causal effects" and propose directions for studies that might better address such questions.

SUBJECTS AND METHODS

Treatment Phase

A detailed description of the research protocol is presented elsewhere.[8,9] A brief overview of procedures in the short-term treatment phase is presented herein.

Patients

Study patients had to be between the ages of 21 and 60 years, meet Research Diagnostic Criteria (RDC)[19] for a current episode of definite MDD, have a minimum score of 14 on an amended version of the 17-item Hamilton Rating Scale for Depression (HRSD),[20,21] and provide informed consent. There were additional exclusion criteria.[8] Two hundred fifty patients passed all criteria and were randomized to treatment; 239 patients actually entered treatment.

Procedures

At each of three research sites (George Washington University, Washington, DC, University of Pittsburgh (Pa), and University of Oklahoma, Oklahoma City), patients were randomly assigned to one of the four 16-week treatment conditions: CBT, IPT, imipramine plus CM, or placebo plus CM. Experienced therapists received further training in their respective approaches, and each treatment condition was carried out according to a detailed manual.[2,3,22]

Follow-up Phase

Patients completing the treatment protocol entered the follow-up phase after their last treatment session. For the pharmacotherapy conditions, medication dosages were gradually reduced and patients received one to two tapering sessions during the first 4 to 6 weeks of the follow-up period. Patients not completing treatment were also included in the follow-up. As noted, the follow-up was naturalistic, with no experimental control over further treatment patients might receive. Follow-up evaluations were scheduled at 6, 12, and 18 months after treatment completion or following the point at which treatment would have been completed for those patients who dropped out or were withdrawn from the study.

The same procedures for treatment referral at the end of the short-term phase were followed in all treatment conditions: patients who were doing well, but interested in further treatment, were encouraged to wait a few months, but they were provided with referrals if they did not want to wait. Patients who were symptomatic were provided with referrals in as standard a fashion as possible for patients in the different treatment conditions. Patients were not permitted to return to their study therapist following completion of the short-term phase.

Assessment

Patients were assessed at each follow-up evaluation using the Longitudinal Interval Follow-up Evaluation II (LIFE-II-II), developed to assess the longitudinal course of psychiatric disorders.[23] The LIFE-II includes a semistructured interview that generates detailed information for retrospective ratings of psychopathologic course over the previous 6 months. Weekly psychiatric status ratings (PSRs) are made on a six-point scale for episodic affective disorders, ranging from meeting RDC criteria for the index episode (rating of 5 or 6) to no residual symptoms (rating of 1). Ratings for all other disorders, including chronic minor and intermittent depressive disorders, are made on a three-point scale. All RDC disorders present at intake into the study or developed during the follow-up phase were rated. Detailed information regarding treatment received during the follow-up period was assessed separately.

A videotape interrater reliability study of the LIFE-II was conducted in which clinical evaluators at all sites (n=7) rated the same videotaped LIFE-II interviews for 12 patients. Rater agreement was assessed on major course variables and was consistently good to excellent (intraclass correlations and κs ranging from .82 to .93).

Evaluation of Outcome

Recovery was defined as stable symptomatic remission from MDD, requiring LIFE-II PSRs of 1 or 2 (minimal or no symptoms) for a minimum of 8 consecutive weeks following completion of

33% for IPT and placebo plus CM, and 50% for imipramine plus CM. At 1 year (not shown) 21% of the recovered sample had relapsed, including 9% of patients in the CBT group, 24% of patients in the IPT group, 28% of patients in the imipramine plus CM group, and 25% of patients in the placebo plus CM group. The mean number of weeks that patients in the recovered sample were asymptomatic, ie, without clinically significant symptoms on any affective disorder scale (including minor and intermittent depressive disorders) over the 78 weeks of follow-up was 67.0 weeks for recovered patients in the CBT group, 63.0 weeks for recovered patients in the IPT group, 53.2 weeks for recovered patients in the imipramine plus CM group, and 67.0 weeks for recovered patients in the placebo plus CM group (Table 2).

As noted, we required 8 weeks without symptoms for our primary definition of recovery. Given the common use of cross-sectional definitions of recovery in clinical trials, including our own report of treatment outcome,[9] however, relapse rates for a sample so defined are of interest. In addition, our requirement of a stable recovery during the first 8 weeks of follow-up means that patients who are improved at termination but have an early relapse (during the first 8 weeks) are not included in the recovered sample and are thus not counted in relapse rates. This could result in an underestimate of relapse over follow-up particularly for imipramine plus CM, by missing patients who relapse following discontinuation of treatment with medication. The following rates of MDD relapse were found during the 18 months of follow-up in the sample of patients with an HRSD of 6 or less at termination: seven (39%) of 18 for CBT; 14 (56%) of 25 for IPT; 10 (45%) of 22 for imipramine plus CM; and five (42%) of 12 for placebo plus CM. Interestingly, only two of the patients in the imipramine plus CM group with an HRSD of 6 or less at termination relapsed during the first 8 weeks of follow-up.

COMMENT

The most significant aspect of the findings reported herein concerns the relatively small number of patients who have an optimal course, ie, achieve a full recovery following 16 weeks of treatment and then remain well during the 18-month follow-up period. Although most patients in the study showed improvement,[9] of all those who entered treatment and had complete follow-up data, only 39% met our stringent recovery criterion, and only 24% both recovered and remained well (no MDD relapse).

There were no significant differences among any of the treatment conditions in terms of the proportion of the original sample who recovered and remained well. For the subsample of patients who are less severely depressed/impaired at pretreatment, the two psychotherapy conditions seemed to have a slightly better outcome. Further studies investigating a possible advantage of the psychotherapies for less impaired patients, when short- and longer-term results are considered, would be useful.

The findings also indicated that the probability of relapse (MDD) did not differ substantially for patients recovering in the different treatment conditions, ranging from 33% to 50%. Patients recovering in all conditions are at a fairly high risk of relapse. Despite these rates of relapse, however, we find that on average, patients in the recovered sample were asymptomatic the majority of the time over follow-up (Table 2). Since about a third of those patients received further treatment during the follow-up, this does not represent a totally untreated course.

Considering indexes of outcome other than MDD relapse (ie, receiving treatment, weeks without symptoms), we did not find any indications of an advantage for patients recovering in IPT. In their 1-year follow-up of patients treated with IPT, amitriptyline hydrochloride, or the combination, Weissman and colleagues[18] similarly found no differences for IPT on clinical symptoms of depression, but they did find a main effect for IPT on measures of social functioning. In cross-sectional analyses of social functioning for the total sample in the TDCRP,[26] no significant differences were found among any of the treatment conditions in social functioning at 6 or 12 months. At 18 months, IPT was significantly superior to imipramine plus CM and differed at a trend level from CBT on global social functioning, but it did not differ significantly from placebo plus CM. Further work on mode-specific effects at follow-up are in progress and will be reported separately.

Patients recovering in CBT had the lowest rates of receiving treatment for depression during the follow-up, and particularly at the 1-year point, they had a low rate of relapse when defined as MDD or treatment (14% compared with 50% for imipramine plus CM, 43% for IPT, and 31% for placebo plus CM). Previous follow-up studies of CBT have reported better outcomes (following termination from treatment) for CBT-treated patients than for patients treated with tricyclic antidepressants on a variety of indexes, including relapse rates.[13-17] The consistency of the findings has encouraged optimism regarding the prophylactic value of CBT.[27] However, the possibility that CBT selects healthier patients (with a lower latent risk of relapse) for recovery, compared with those recovering with tricyclic antidepressant treatment, is an equally plausible explanation for these findings. In our study, although we could not detect differences on most clinically relevant variables for patients recovering in the different treatment conditions (eg, HRSD and GAS pretreatment and termination scores, number of prior episodes), we did find that proportionally more recovered patients in the imipramine plus CM group entered the study with a GAS score of 50 or less (more impaired). Another consideration is the performance of the placebo plus CM condition in the current study, that did not show notable differences from CBT on any measures over follow-up. The previous studies cited did not include a placebo group. Thus, despite the consistently better outcome of CBT as compared with tricyclic antidepressants reported in these studies, the ability of CBT to provide prophylaxis remains an open question.

This question cannot be answered by post–short-term treatment naturalistic follow-up studies. If enduring effects can be tested, this will require new designs. Other approaches might include studying alterations in the course of individual patients, studying the relationship between hypothesized mechanisms of change and course, or examining the relationship between the dose or competency of treatment delivered and subsequent course. None of these approaches, however, is without its own methodologic limitations.

What is clear from our findings is that 16 weeks of these particular treatments is insufficient treatment to achieve full recovery and lasting remission for most outpatients with MDD. This finding is similar to that of other studies. The recent report on maintenance treatments for recurrent depression, for example, also documents the need for further treatment for recovered patients following treatment with a combination of IPT and imipramine.[28] A recurrence rate of 74% in the first 2 years was found for patients in the inactive maintenance treatment cell (medication clinic and placebo). The advantages of continuing pharmacotherapy following recovery were evident in this maintenance study as well as earlier studies.[29] Although the strongest effects

in preventing relapse were found for pharmacotherapy (imipramine), it is also of interest that one session of IPT a month was found to delay relapse significantly in patients not receiving active medication.[28]

The increasing evidence for high rates of relapse and chronicity in patients with depression argues for continued research directed at improving strategies for initial and maintenance treatment. The efficacy of longer periods of psychotherapy, as an initial treatment or as a maintenance treatment, and alone or in combination with pharmacotherapy, is an important question for such research.

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