Interpersonal Psychotherapy and Antidepressant Medication: Evaluation of a Sequential Treatment Strategy in Women With Recurrent Major Depression

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Background: Few data are available to guide treatment selection in major depression. With increasing pressure to maximize the efficiency and minimize the costs of treatment, it is important to have information that could guide treatment selection or point to treatment strategies that have a high probability of success.

Method: We used a successive cohort approach to compare 2 highly similar groups of women with recurrent unipolar disorder (DSM-III-R or DSM-IV): one in which the combination of interpersonal psychotherapy (IPT) and pharmacotherapy was initiated at the outset of treatment and a second in which IPT alone was provided first and only those who did not remit with IPT alone were offered the combination treatment.

Results: In the group in which the combination was initiated at the outset of treatment (N = 180), the remission rate was 66%, comparable to the remission rate observed in most outpatient treatment studies of major depression. In contrast, among the women in the second cohort who were first treated with IPT alone and only those who did not remit were given combination therapy (N = 159), the remission rate was 79%, significantly greater than that observed in the group that received combination treatment from the outset ($\chi^2 = 6.55$, p = .02).

Conclusion: These results suggest that the strategy of offering IPT to women with recurrent unipolar disorder and, in the absence of remission, adding antidepressant pharmacotherapy can be a highly effective treatment, one that may be particularly attractive to women in the childbearing years. Although slower in its onset of action, this sequential strategy is likely to enable the clear majority of such women to achieve a full remission of depressive symptoms.

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A series of key features should be considered when evaluating acute treatments for major depression, including (1) rapidity of onset of action, (2) rapidity and completeness of remission, (3) the proportion of individuals exposed who are able to achieve a full remission of symptoms, and, perhaps the most important, (4) the proportion able to sustain that remission. A substantial body of evidence[1,2] attests to the more rapid onset of action of antidepressant pharmacotherapy relative to the depression-specific psychotherapies, such as interpersonal psychotherapy (IPT)[3] and cognitive therapy.[4] The literature also suggests that pharmacotherapy alone probably leads to a more rapid and, perhaps, to a more complete remission of symptoms than does psychotherapy alone. It is less clear whether a greater proportion of individuals achieve remission with pharmacotherapy compared with depression-specific psychotherapy, unless the analysis is restricted to those with more severe symptomatology, e.g., a Hamilton Rating Scale for Depression (HAM-D) score ≥ 20.[1] There have been relatively few studies that compare the combination of pharmacotherapy and psychotherapy with either treatment alone. Those that have been reported suggest remission rates may be somewhat better for combination treatment compared with psychotherapy or pharmacotherapy alone. Hollon et al.[5] found remission rates of 52%, 32%, and 33%, respectively, for the combination of cognitive therapy and imipramine, imipramine alone, and cognitive therapy alone among all subjects entering the 12-week acute phase of their trial. In a "mega-analysis" of 595 cases, Thase et al.,[6] found remission rates of 48% and 37%, respectively, for the combination of IPT and imipramine versus IPT alone.

In the course of conducting 2 separate depression treatment trials, 1 in which women with recurrent unipolar de-

pression were treated with IPT alone and only those who did not remit with IPT alone had pharmacotherapy added to the treatment regimen, and a second in which subjects were treated with the combination of IPT and pharmacotherapy from the outset of treatment, we were struck by the greater success of the sequential treatment approach. We therefore decided to do a more formal comparison of these 2 approaches to treatment. We anticipated that a treatment strategy of IPT alone, followed by the combination of IPT plus antidepressant in those not achieving remission with IPT alone, would be relatively less efficient with respect to speed of remission for the overall group, but relatively more efficacious with respect to the proportion of subjects able to achieve a sustained remission.

METHOD

Using these 2 successive cohorts treated in our clinic, we compared the proportion remitting and speed of remission among women with recurrent unipolar depression who received sequential combination treatment (IPT alone, then IPT and pharmacotherapy in those not remitting with IPT alone) in our ongoing study of maintenance psychotherapy in women (sequential treatment study)[7–9] with the same outcomes in a comparison group who received combination therapy (both IPT and pharmacotherapy) at the outset of their acute treatment in our previously reported maintenance therapies in recurrent depression study (combination treatment study).[10] Screening criteria, initial clinical evaluation, ongoing clinical monitoring, and the definition of remission were similar in the 2 studies.

Screening Criteria

The screening criteria for the 2 protocols were nearly identical. To enter the sequential treatment protocol, women between the ages of 20 and 60 years were required to be in their second* or greater episode of unipolar major depression. To enter the combination treatment protocol, subjects between ages 21 and 65 years were required to be in their third or greater episode. In both protocols, the immediately preceding episode could be no more than 2.5 years before the onset of the present episode. A minimum HAM-D[11] score of 15 and a minimum Raskin Severity of Depression[12] score of 7 were also required. Patients were excluded if they met criteria for any other Axis I diagnosis (except generalized anxiety disorder, panic disorder, or eating disorder NOS) or if they met full criteria for antisocial or borderline personality disorder. Medical exclusions included (1) index episode secondary to the effect of prescribed medication, e.g., reserpine, antihistamines, and (2) the presence of significant medical illness, including cardiovascular disorder, renal or liver disease, epilepsy, untreated hypertension, or unstabilized endocrine disease. Subjects taking oral contraceptives or hormone replacement therapy were not excluded. In both protocols, subjects were excluded if they had any condition considered incompatible with use of the antidepressant to be prescribed (i.e., imipramine or a selective serotonin reuptake inhibitor [SSRI]).

Initial Clinical Evaluation

Following a preliminary evaluation, all patients who appeared to be eligible were evaluated using the Schedule for Affective Disorders and Schizophrenia (SADS).[13] After 1995, the Structured Clinical Interview for DSM-III-R[14] and DSM-IV[15] (SCID) replaced the SADS as our primary diagnostic instrument. Thus, all subjects in the combination treatment protocol and the first 50 subjects in the sequential treatment protocol completed the SADS, and the remaining 109 completed the SCID. Those found to meet criteria for a major depressive episode and the historical requirements for previous episodes and clear remissions then met with the project coordinator or their primary clinician, who explained the study protocol and obtained informed consent to continued evaluation and study participation. Any antidepressant medication being taken at the time of initial evaluation was withdrawn over a period of 2 or more weeks (depending on the specific compound), and those subjects were reevaluated to ensure that they continued to meet study requirements with respect to severity of depression.

Clinical Monitoring and Definition of Remission

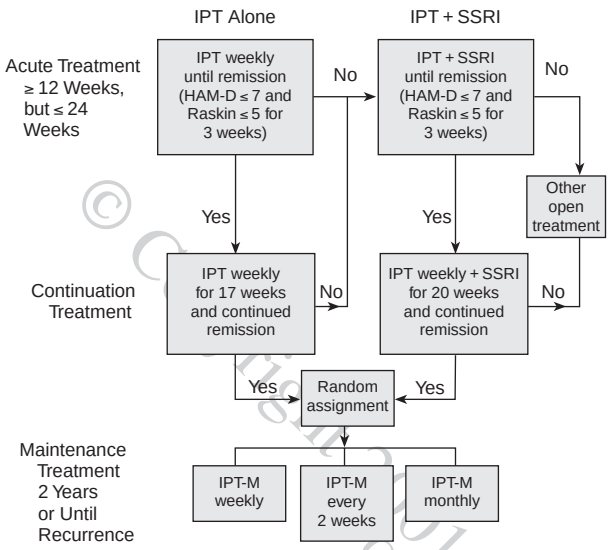
Clinical monitoring of patients and the definition of remission were identical in the 2 protocols. Clinical status was monitored at each clinic visit with the HAM-D, Raskin, Beck Depression Inventory,[4] and Global Assessment Scale (GAS)[16] ratings; however, determination of nonresponse was based on HAM-D scores. Remission was defined by a HAM-D score of ≤ 7, a Raskin score of ≤ 5 for 3 consecutive weeks, and a clinical consensus that the index episode had remitted. If the patient did not obtain at least a 50% reduction in her admission HAM-D score after 24 weeks of treatment or if the patient experienced a relapse, the patient was terminated from the trial and other standard pharmacotherapies for depression were prescribed.

The Sequential Treatment Protocol: Maintenance Psychotherapy in Women

The subjects who represent the principal focus of this report were drawn from an ongoing protocol that was designed to explore the relative efficacy of 3 frequencies of

*In fact, all but one of the subjects on whom definitive acute outcomes are currently available were in their third or greater episode at the time of study entry. The single subject in her second episode was not included in the present analysis in order to make these subjects comparable to the second cohort.

Figure 1. Design of Maintenance Psychotherapy in Women (Sequential Treatment)[a]



[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression, IPT = interpersonal therapy, IPT-M = maintenance IPT, Raskin = Raskin Severity of Depression scale, SSRI = selective serotonin reuptake inhibitor.

maintenance interpersonal psychotherapy (IPT-M)[17] in preventing or delaying a recurrence of illness in women with recurrent unipolar depression. All subjects are initially treated with interpersonal psychotherapy[3] alone. Those achieving sustained remission, defined as 8 consecutive weeks with a HAM-D score ≤ 7, with IPT alone are then randomly assigned to 1 of 3 frequencies of IPT-M sessions for a period of 2 years. Subjects who fail to achieve or sustain a remission with IPT alone and agree to the addition of antidepressant medication are given antidepressant medication in addition to IPT (Figure 1).

IPT alone treatment. Patients were treated weekly with IPT until remission of their episode or a determination of nonresponse was made. If patients were not responding to weekly sessions of IPT (defined as less than a 33% symptom reduction from baseline HAM-D score within 4 weeks of treatment initiation), twice-weekly sessions were scheduled. Nonresponse was defined according to the following algorithm: less than 25% symptom reduction from baseline HAM-D score by week 6, less than 50% symptom reduction after 4 weeks of weekly IPT followed by 4 weeks of twice-weekly IPT, less than 50% symptom reduction by week 12, or absence of remission following 24 weeks of IPT alone. At the earliest point at which a subject met the criteria for nonresponse to IPT alone, she was offered the option of having antidepressant pharmacotherapy added to her treatment regimen. The protocol requires evidence of a sustained remission (8 consecutive weeks of continuation treatment during which HAM-D scores remain in the remission range as defined above) for entry into the experimental maintenance phase. Patients who achieved remission rapidly were required to have weekly IPT sessions for a minimum of 12 weeks prior to being considered in remission. In general, patients were treated for 12 to 20 weeks on a weekly basis before achieving remission (see Figure 1).

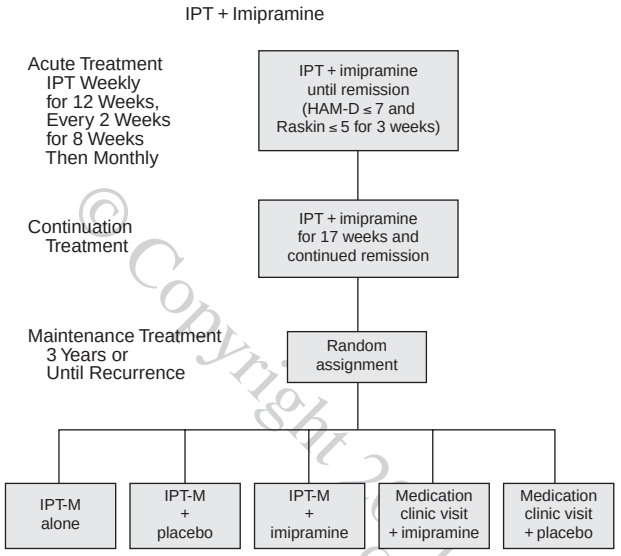
IPT plus antidepressant treatment. Subjects who did not remit with IPT alone were offered treatment with weekly IPT plus an SSRI until remission was achieved. Typically, pharmacotherapy began with 10 to 20 mg/day of fluoxetine. Dosage adjustments were made on the basis of individual responsiveness and tolerability. If the patient experienced difficulty with sleep after the medication was prescribed, the time and dosage of medication were adjusted. Three patients received adjunctive trazodone (25 mg in 2 cases and 50 mg in 1 case) for persistent insomnia during acute treatment. One such patient terminated from the acute phase, and the other 2 stabilized and entered the continuation phase with fluoxetine and trazodone. Six women with previous histories of failure to respond to fluoxetine were treated with sertraline (50–250 mg/day). Following acute treatment and symptom remission with IPT plus antidepressant, patients entered a continuation phase during which they received weekly IPT and medication for 20 weeks. At the end of this continuation phase, medication was discontinued and patients continued to receive IPT alone for 6 to 8 weeks before entering the maintenance treatment phase.

The Combination Treatment Protocol: Maintenance Therapies in Recurrent Depression

The protocol from which the comparison subject cohort was derived was designed to explore the relative efficacy of 5 maintenance treatment strategies in preventing or delaying a recurrence of illness in a population of male and female patients with recurrent unipolar depression.[10,18] Depressed patients were treated acutely with IPT plus imipramine through the remission and recovery periods. For the present analysis, we examined only female subjects (Figure 2).

IPT plus imipramine treatment. Patients received an acute treatment regimen consisting of a combination of IPT plus imipramine hydrochloride (target range, 150–300 mg/day; target combined plasma level, > 125 ng/mL) until remission of the current episode. IPT sessions were scheduled weekly for 12 weeks, then every 2 weeks for 8 weeks, and then monthly. If patients did not respond to the combination of IPT and imipramine, depending on clinical presentation, augmentation with perphenazine, liothyronine (T_3), or lithium was initiated. All augmentation medications were required to be discontinued prior to declaration of remission status. Patients who stabilized rapidly were required to have weekly sessions for a mini-

Figure 2. Design of Maintenance Therapies in Recurrent Depression (Combination Treatment)[a]



[a]Based on Frank et al.[10]

mum of 12 weeks. In general, patients were treated for 12 to 20 weeks before reaching remission, after which they entered a 17-week continuation treatment phase with IPT sessions plus imipramine, during which both rating scale scores and imipramine dosages were required to remain stable (see Figure 2).

Clinical Environment and Clinician Training

Both studies under consideration in this report were conducted in the Depression and Manic-Depression Prevention Clinic (DMDPC) within the Western Psychiatric Institute of the University of Pittsburgh Medical Center (Pittsburgh, Pa.). The first author (E.F.) has been the director of this clinic since its inception, and the majority of the clinic staff (physicians, therapists, and independent clinical evaluators) have remained constant throughout the period covered by the 2 studies described here, thus adding to our confidence in the comparability of the treatment environment, the treatment approach of the IPT therapists, and the clinical assessments. The first combination treatment study occurred between July 1982 and November 1989. The sequential treatment study occurred between September 1992 and October 1998. Under the auspices of our Mental Health Clinical Research Center grant (D.J.K.), we have conducted regular recalibration of evaluators on all assessment instruments used in DMDPC protocols and maintain interrater agreement levels on instruments such as the HAM-D of ≥ 0.90.

All IPT therapists within the DMDPC received their training either from the developers of the treatment (G. L. Klerman, M.D.; M. M. Weissman, Ph.D.; B. J. Rounsaville, M.D.; E. S. Chevron, M.A.) or from Cleon Cornes, M.D., a certified IPT trainer, who has conducted group supervision of all IPT therapists in the DMDPC every 2 weeks throughout the period covered by the 2 protocols described here. Thus, we believe that the quality of IPT treatment provided has remained relatively constant throughout the period under consideration.

Statistical Methods

Baseline demographic and clinical characteristics of the 2 cohorts were compared with group t tests for continuous variables and chi-square tests for categorical data. Although both groups are similar in recruitment and study procedures, the 2 groups of depressed women are not equivalent on all demographic, clinical, and clinical history variables. Accordingly, we examined the effects of potentially influential variables and controlled for clinical differences when testing speed of remission in the 2 cohorts. Remission rates were calculated for each cohort and compared using the chi-square test for contingency tables. Finally, we examined covariates of time to remission for baseline HAM-D score, baseline GAS score, duration of index episode, number of previous episodes, age at initial onset, age at study entry, and number of IPT sessions during acute treatment using a Cox proportional hazards model. These analyses were examined using the Wald chi-square statistic.

RESULTS

Demographic and clinical characteristics of the 2 cohorts are presented in Table 1. While the cohorts are reasonably similar with respect to age at entry and number of previous episodes, the sequentially treated cohort had significantly lower baseline HAM-D scores and were less likely to have the index episode categorized as endogenous according to Research Diagnostic Criteria. On the other hand, members of this cohort had been ill slightly longer at the outset of treatment. It is noteworthy that at initiation of medication in the sequential treatment protocol, subjects' HAM-D scores remained essentially identical to their baseline scores: the mean ± SD 17-item score changed only from 18.6 ± 3.2 to 18.0 ± 4.6.

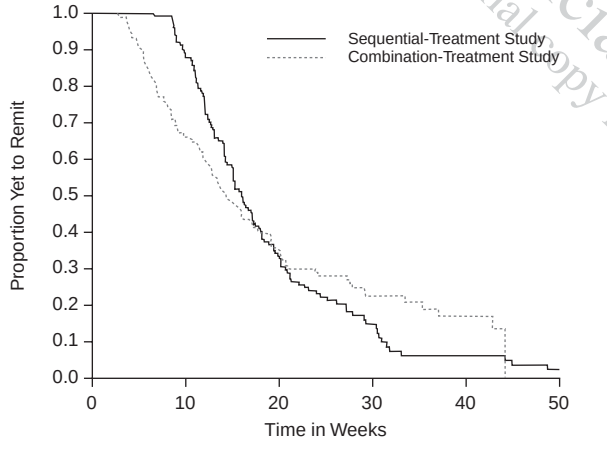
Of the 159 subjects for whom we currently have definitive outcomes in the sequential treatment protocol, 79 (49.7%) achieved remission with IPT alone, 17 dropped out or were discontinued for nonadherence to the protocol before a determination of remission status could be made, and 63 were deemed nonresponders to IPT alone, 58 of whom subsequently entered the IPT plus antidepressant phase. Five subjects did not enter the combination treatment phase: 1 because of pregnancy, 2 because of a secondary diagnosis, 1 because she required more intensive management than the protocol could provide, and 1 because of nonadherence to protocol requirements. Of the

Table 1. Clinical Characteristics of the 2 Samples[a]

Characteristic	Sequential-Treatment Study (N = 159)	Combination-Treatment Study (N = 180)	Statistic
Age, y	37.3 ± 9.9	39.3 ± 10.5	t = 1.79, p = .07
HAM-D score at study entry	18.6 ± 3.2	22.2 ± 4.4	t = 8.47, p = .0001
GAS score at study entry	54.4 ± 5.7	49.5 ± 8.6	t = 6.15, p = .0001
Raskin score at study entry	8.7 ± 1.3	10.4 ± 1.8	t = 9.80, p < .0001
Age at onset, y	24.2 ± 8.7	26.7 ± 10.1	t = 2.41, p = .02
Median	22.0	25.0	
Duration of index episode, wk[b]	27.2 ± 20.8	23.1 ± 17.5	t = 1.36, p = .17
Median	21.0	17.0	
Number of previous episodes	7.3 ± 9.5	6.2 ± 5.6	t = 1.33, p = .18
Median	4.0	4.0	
Endogenous depression, N (%)			
Absent	76 (48)	19 (10)	χ^2 = 71.03, p = .0001
Probable	12 (8)	58 (32)	
Definite	65 (41)	102 (57)	
Not categorized	6 (3)	1 (1)	
HAM-D score at initiation of medication	18.0 ± 4.6	22.2 ± 4.4	t = 6.13, p = .0001
Medication dosage, mg/d	Fluoxetine, 21.6 ± 7.8	Imipramine, 202 ± 79.4	

[a]Abbreviation: GAS = Global Assessment Scale. Data presented as mean ± SD unless otherwise indicated.
[b]Log transformation.

Figure 3. Time to Remission



58 women who were offered combination treatment, 46 (79.3%) achieved criteria for remission and entered the continuation treatment phase. Of the 12 patients who failed to reach the continuation phase, 9 did not respond fully to the combination of IPT plus antidepressant and 3 patients were terminated from the study (1 for noncompliance with the protocol and 2 because they preferred other treatment). When all 159 subjects are considered, the overall proportion remitting is 78.6%.

Of the 180 women who entered the earlier combination treatment protocol, in which IPT plus imipramine were used at the outset of treatment, 119 (66.1%) achieved criteria for remission and entered the continuation treatment phase. Of the 61 patients who failed to reach the continuation phase, 35 did not respond fully to the combination of imipramine and IPT, 9 dropped out of the study or were terminated for noncompliance with the protocol, 7 developed intolerable side effects, 1 developed a medical condition incompatible with continued imipramine therapy, 2 developed secondary psychiatric illness, and 7 failed to reach the continuation phase for other reasons.

When remission rates are examined, the combination treatment strategy yields a significantly lower remission rate (66.1%) than the sequential treatment strategy (78.6%) (χ^2 = 6.55, p = .02). By design, when all subjects are considered (including nonresponders and dropouts), median time to remission is, of course, longer for the sequential treatment strategy (15.9 weeks) than for immediate combination treatment (14.1 weeks). The survival curves (Figure 3) illustrate this effect. The proportionality assumption of a Cox regression is violated. Thus, study group was used as a strata variable. Using a backward-stepping Cox proportional hazards model, 2 covariates of time to remission were detected: age at onset of depressive illness (p < .005) and baseline HAM-D score (p < .001). Women with earlier age at onset and higher baseline HAM-D scores required more time to achieve remission.

Because the sequentially treated subjects from the study of maintenance psychotherapy in women, as a group, exhibited lower baseline severity of depression, which alone might explain their superior response, we further examined this possibility by dividing both study populations into higher and lower severity cohorts using a baseline HAM-D score of ≥ 20 to define the higher severity cohorts. Interestingly, we found that significantly more of the high severity patients in the sequential treatment condition remitted compared with the high severity patients in the combination-treatment condition (81.1% vs. 58.0%, p < .02). The proportions remitting in the low severity groups did not differ (77.9% vs. 79.4%, p = .80).

DISCUSSION

We have long been interested in examining IPT alone, medication alone, and the combination of these treatments in the treatment of recurrent unipolar depression. A design feature of one of our ongoing depression studies allowed us a unique opportunity to treat a group of women with recurrent depression first with IPT alone and then add medication sequentially only for those women who did not remit with psychotherapy alone. We were struck by the high overall remission rate that this strategy

appeared to yield. To place this sequential treatment strategy in context, we compared outcomes using this strategy with those of women who had received combination treatment of IPT plus imipramine from the outset of their treatment in an earlier trial carried out by the same treatment team in the same setting a few years earlier. It must, of course, be acknowledged that these 2 groups of subjects do not represent random samples from a single population; however, the similarity of the criteria by which they were selected and the setting in which they were treated make it reasonable to think about why their outcomes differed in what we see as a clinically meaningful way. Furthermore, it must be acknowledged that the absence of a control comparison equated for therapeutic contact time limits the interpretation of the findings.

Because these successive cohorts are not perfectly matched, despite meeting essentially the same inclusion and exclusion criteria, we must consider a number of alternative explanations for the variation observed in remission rates beyond the difference in treatment strategies employed. The higher remission rate observed in the sequentially treated subjects might simply be a function of differences in baseline severity of depression: more subjects in the sequential treatment cohort responded because their depressions were less severe. This seems an unlikely explanation given the fact that it was only among the more severely depressed subjects that the sequential strategy was superior.

A second possibility is that SSRIs are more efficacious than imipramine and that we would have observed the same difference between the cohorts if the sequential group had been treated with the combination of SSRI and IPT from the outset of treatment. While this explanation remains plausible, it must be noted that direct comparisons of SSRIs and tricyclics in recent meta-analyses[19,20] have not revealed differences in efficacy.

A third possibility is that the differences in remission rates are attributable to differences in the frequency and amount of IPT. The sequential treatment group was given IPT weekly until remission with the possibility of twice-weekly sessions if improvement failed to reach prespecified levels, whereas the immediate combination treatment group received IPT weekly for 12 weeks, then every 2 weeks for 8 weeks, and then monthly to the end of continuation treatment. It seems unlikely that this explains the difference since the average number of sessions prior to remission was 13 and 8, respectively, for the sequential and immediate combination groups, and the median time to remission (14.1 weeks) came just at the point at which subjects in the immediate combination group began sessions every 2 weeks.

Perhaps there were simply more spontaneous remissions in the sequentially treated group. This is a possibility that must be considered, given that the sequentially treated group had been ill slightly longer when they entered the protocol and, by design, spent more time under protocol treatment. The likelihood that this explains the difference in proportion remitting, however, is greatly mitigated by the rapid and sustained remissions achieved in those subjects in whom medication was added to IPT, most of whom had evidenced little to no symptom reduction prior to the initiation of pharmacotherapy.

Another possibility is that the subjects in the 2 cohorts made different attributions about their likelihood of responding. Those in the sequential treatment group, i.e., those who had medication added to their treatment, may have believed they were being "rescued" by the addition of medication. On the other hand, given the negative attributional style typical of acutely depressed individuals, it seems equally probable that the failure of the first treatment offered to bring about remission may have made them even more hopeless, thus producing negative expectations about the likelihood of responding to the combination.

A final possibility, and the one we think most likely, is that this is a true difference between the treatment strategies. In the sequential treatment strategy, initial IPT acts like a sieve, selecting out those subjects who truly need pharmacotherapy to achieve remission and remain well. Indeed, we previously observed a virtually identical rate of remission (78.0%) with sequential treatment in a mixed-sex cohort treated with IPT followed by imipramine or fluoxetine.[6] Thus, it would appear that the higher remission rate observed in the sequential treatment group is most likely a function of the fact that the sequence first captures all those who can achieve remission with IPT alone (about 50%) and selects out a remaining group who are very responsive to the combination.

If it could be demonstrated in a randomized trial that the sequential strategy of psychotherapy alone followed by the addition of drug yields a significantly higher remission rate than other treatments or strategies, in a not appreciably longer period of time, there would be a number of reasons to recommend this strategy. First, it appears to yield a significantly higher ultimate remission rate than either IPT alone, medication alone,[1] or the immediate combination treatment strategy described above. Second, it would be less costly than providing combination treatment from the outset (although admittedly not less costly than medication alone). Third, and most important, our group has repeatedly shown that among patients with recurrent depression, the treatment that gets the patient well has a very high probability of keeping the patient well.[10,21–23] Early results from the maintenance phase of the ongoing trial of maintenance psychotherapy of women suggest that this maxim can be applied to interpersonal psychotherapy as well. Thus far, the overall recurrence rate observed over the course of the 2-year maintenance treatment phase among those women who achieved remission with IPT alone (27.9%) is remarkably low

given the highly recurrent nature (a median of 5 lifetime episodes) of the depressive illnesses from which these women suffer. By sequencing IPT and IPT plus medication, many more patients might be able to not only achieve remission but also maintain wellness without chronic medication exposure. This should be of particular importance to women in the childbearing years when maintenance pharmacotherapy is probably best avoided during conception, pregnancy, and lactation. In an era when quality of life under various treatment conditions is taking on increasing importance in the minds of clinicians and patients (if not cost managers), the sequential treatment strategy, offering the possibility of sustained remission without medication to a large subpopulation of recurrently depressed women, seems a strategy worth trying.

Drug names: fluoxetine (Prozac), liothyronine (Cytomel), perphenazine (Trilafon and others), reserpine (Serpasil and others), sertraline (Zoloft), trazodone (Desyrel and others).

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