

Research report

The efficacy of imipramine and psychotherapy in early-onset chronic depression: a reanalysis of the National Institute of Mental Health Treatment of Depression Collaborative Research Program

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Abstract

The authors compared the effectiveness of Cognitive Behavioral Therapy (CBT), Interpersonal Psychotherapy (IPT), Imipramine Clinical Management (ICM) to Placebo Clinical Management (PCM) for outpatients with early-onset chronic depression ($N = 65$) in the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (TDRP). The post-treatment depression scores of the CBT, IPT, and ICM groups were not significantly different from the PCM group. We did not find a relationship between the duration of Major Depression and response to a specific treatment. Studies are needed to determine if combining psychotherapy with medication improves social functioning and enhances the quality of life for patients with chronic depression. © 1997 Elsevier Science B.V.

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1. Introduction

Depression which begins early in life and endures throughout the life cycle is a disabling disorder whose symptomatic severity fluctuates considerably over time (Akiskal, 1992). Traditionally, these patients were conceptualized as having a characterological neurosis (Arieti and Bemporad, 1978). Though long-term insight-oriented psychotherapy

was the recommended treatment (Bemporad, 1983), its efficacy was not rigorously tested.

The advent of standardized, operationalized, specific, short-term psychotherapies for depression, along with the increased reliability of assessment instruments, enabled investigators to rigorously test the efficacy of psychotherapy for unipolar depression (Elkin et al., 1985).

We are unaware of psychotherapy studies that have tested the efficacy of psychotherapy for early-onset chronic depression, but uncontrolled psychotherapy studies have been reported. Luborsky et al. (1996), in a study of short-term dynamic psychother-

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apy of patients with chronic and non-chronic Major Depression found that duration of depression accounted for less than 1% of the treatment response outcome. However, Thase et al. (1994) found that acutely depressed patients, treated with cognitive behavioral therapy, had significantly lower depression scores than patients with chronic depression.

Numerous placebo-controlled studies (Kocsis et al., 1988; Stewart, 1993; Versiani, 1994; Bakish et al., 1993; Hellerstein et al., 1993; Bersani et al., 1991) have demonstrated the effectiveness of antidepressants for various subtypes of chronic depression.

To our knowledge, the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (TDCR) is the only published, large-scale, placebo-controlled study of psychotherapy for outpatients with unipolar depression (Elkin et al., 1989). The released public access tape of this study provided us with an opportunity to determine the efficacy of short-term psychotherapy for early-onset chronic depression. Since ICM was part of the TDCR study, its efficacy was also tested.

2. Methods

2.1. Sample and treatment

Sample selection and patient treatment have been described in detail previously (Elkin et al., 1989). Briefly, the NIMH Treatment of Depression Collaborative Research Program was a 16-week, multi-site, randomized study which compared Imipramine Clinical Management (ICM), Cognitive Behavior Therapy (CBT) and Interpersonal Psychotherapy (IPT), with Placebo Case Management (PCM) in the treatment of unipolar depression. The Clinical Management (CM) component of the Placebo and Imipramine conditions was intended to monitor patients' clinical status, manage side-effects, and provide "minimal supportive therapy" (Elkin et al., 1989).

2.2. Assessment

The Schedule of Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) was used to make our categorical diagnoses. We defined early-onset chronic depression as an episode of

Major Depression beginning before age twenty-one and lasting longer than two years. The age threshold for early-onset categorization was taken from DSM-III-R (American Psychiatric Association, 1987).

2.3. Analyses

The relative efficacy of each specific treatment, for the early-onset chronic group, was tested using stepwise, hierarchical, multiple regression procedures. The outcome variables were the: Global Assessment Scale (GAS) (Endicott et al., 1976), 17-Item version of the Hamilton Rating Scale for Depression (Ham-d) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck et al., 1961). The scores at the last visit were used for the patients who dropped out or were withdrawn from the study. Since Klein and Ross (1993) and Elkin et al. (1995) found baseline depression to be a strong predictor of outcome, pretreatment depression scores were entered at the first step; treatment contrasts (ICM, IPT, CBT, vs PCM) at the second step.

Categorical response/non-response was tested for differences between each psychotherapy and PCM by a 2×2 Chi-Square test. Univariate statistics were analyzed using the *t* and *F* statistics.

Although the main aim of this study was to examine the relative efficacy of psychotherapy, we were also interested in determining how much of the outcome variance was explained by the duration of Major Depression. Thus, a second series of multiple regression analyses were conducted, which included patients with and without early-onset chronic depression ($N = 204$). Predictor variables were entered in the following steps: (1) Baseline depression score; (2) age; (3) duration of Major Depression; (4) treatment group (ICM, IPT, CBT vs. PCM); and (5) interaction of treatment group and duration of Major Depression.

All *P*-values reported are 2-tailed. All variance estimates are standard deviations.

3. Results

The data was derived from 65 patients with early-onset Major Depression (RDC) who completed at

least 3.5 weeks of treatment. This subgroup includes 7 (11%) patients who dropped out or were withdrawn after 3.5 weeks of treatment. In this subsample, the last score obtained, either at interim or early termination of evaluation, was used.

The mean age of the subsample was 31.3 (6.4) and the mean duration of Major Depression was 15.9 (7.9) years. Forty percent (26/65) met criteria for Intermittent Depression. When the treatment groups were compared by ANOVA, no significant pre-treatment differences in mean Ham-d scores were detected ($F = 0.15$, $P = \text{NS}$) (Table 1).

To determine the effect of treatment on three outcome measures (GAS, BDI and Ham-d), predic-

tor variables were entered into a regression analysis in the following steps: (1) the equivalent baseline score for the outcome measure; (2) three dummy variables for each treatment versus PCM comparison.

The R -squares of the BDI and Ham-d measures were significant, indicating that the pre-treatment depression severity accounted for a meaningful amount of the outcome variance. However, the baseline GAS scores did not significantly predict endpoint GAS scores.

The second step examined the main effect of treatment assignment after adjusting for pre-score differences. The partial regression coefficients scores were not significant for the dummy variables representing each treatment versus PCM contrast (Table 2).

To determine the impact of duration of Major Depression on outcome (Ham-d) for patients with and without early-onset chronic depression, a second series of multiregression analyses were conducted (Table 3). The following variables were entered in a stepwise method: baseline Ham-d score, age, duration of Major Depression, treatment group, and the interaction between duration of Major Depression

Table 1
Pre-treatment and post-treatment Ham-d scores

	Pre-treatment		Post-treatment	
	Mean	S.D.	Mean	S.D.
CBT ($N = 16$)	19.4	4.5	9.5	7.2
IPT ($N = 14$)	18.6	5.1	10.3	8.4
PCM ($N = 15$)	18.5	4.4	9.5	5.7
ICM ($N = 20$)	18.5	4.4	10.3	7.7

Table 2
Stepwise multi regression analysis of treatment response among patients with early-onset chronic depression

Enter	Outcome variable	Treatment groups	R^2 change	F change	P	B^a	SE
Baseline score treatment	GAS		0.02	1.4	0.25	−0.17	0.22
		Overall	0.007	0.14	0.93	0.22	0.20
		ICM/PCM				1.6	3.8
		IPT/PCM				1.2	4.1
		CBT/PCM				−0.63	4.0
Baseline Score Treatment	BDI		0.11	8.1	0.006	0.44	0.25
		Overall	0.01	0.34	0.79	0.45	0.17
		ICM/PCM				0.17	3.6
		IPT/PCM				1.0	3.9
		CBT/PCM				3.3	3.7
Baseline Score Treatment	Ham-d		0.16	11.8	0.001	0.66	0.19
		Overall	0.006	0.14	0.93		
		ICM/PCM				0.79	2.3
		IPT/PCM				0.68	2.5
		CBT/PCM				−0.58	2.4

^a Last step.

Table 3
Stepwise multiregression analysis comparing Ham-d outcome scores of CBT, IPT and PCM by duration of Major Depression

Enter	Outcome variable	R ² change	F change	P	B ^a	SE
	Endpoint					
Baseline score	Ham-d	0.07	14.3	0.002	0.46	0.11
Age		0.003	0.83	0.36	0.01	0.06
Treatment		0.02	1.7	0.17		
Treatment × duration		0.03	2.4	0.07		
<i>Comparisons:</i>						
ICM vs. PCM					0.20	0.11
IPT vs. PCM					0.21	0.11
CBT vs. PCM					0.05	0.11

^a Last step.

Table 4
Treatment response rates

	PCM %	ICM %	CBT %	IPT %	CBT vs. PCM	IPT vs. PCM
Ham-d	27 (4/15)	64 (9/14)	38 (6/16)	35 (5/14)	NS	NS
BDI	60 (9/15)	60 (12/20)	56 (9/16)	50 (7/14)	NS	NS

and treatment group. The baseline Ham-D score was highly predictive of outcome. Neither treatment group nor the interaction of treatment group with duration of illness predicted differential response.

3.1. Recovery analyses

The criteria for recovery was defined as a score of 6 or less on the Ham-D and 9 or less on the BDI. The Ham-D and BDI categorical outcome assessments did not reveal significant differences between PCM and the specific treatments (Table 4). There was a trend finding for ICM to have a higher response rate than PCM, when the Ham-D was used as an outcome measure.

4. Discussion

Among patients with early-onset chronic depression, neither ICM, IPT, nor CBT was significantly superior to PCM. There was an approximately 50%

drop in depression severity, measured by the Ham-d, across all treatments. Generally, patients improved from baseline, but they remained significantly depressed at the end of treatment. The mean post-treatment BDI and Ham-d scores, across all treatment groups, remained in the mild range of depression severity. The post-treatment Ham-d scores for ICM and the psychotherapies differed by less than one point.

Using the BDI categorical criteria for recovery, the proportion of patients who responded was almost identical across the treatment. Though the Ham-d categorical outcome did not find significant differences between treatments, the rate of response to PCM was much lower than that found using the BDI criteria. These results suggest that the arbitrary cutoff scores for defining treatment response were dissimilar for the BDI and Ham-d. The discrepancy may have been due to the different assessment procedures. The Ham-d was measured by a clinical evaluator who was blind to the treatment condition. In contrast, the BDI was completed by patients who were aware of what treatment they received, if they

were randomized to one of the psychotherapy conditions.

As noted above, the results of short-term psychotherapy studies for chronic depression have not been consistent (Thase et al., 1994; Luborsky et al., 1996). Our results replicate Luborsky's finding that duration of Major Depression was a weak predictor of outcome. Because we defined chronic depression as having an onset prior to age 21, our sample had longer duration of illness than reported in these studies. In Luborsky's and Thase's samples, the mean duration of Major Depression was 1.5 years and 1.3 years respectively, compared to 15.9 years in our sample.

Several studies (Stewart et al., 1993; Kocsis et al., 1988; Thase et al., 1996) found imipramine to be more effective than a placebo in the treatment of chronic depression. However, this study did not confirm imipramine's efficacy for this disorder.

The most important liability of this study was that its relatively small size may have limited the power to find significant differences between PCM and the specific treatments. This may explain why the results did not replicate imipramine's efficacy for chronic depression. In addition, we did not examine the influence of the following independent variables: (1) site differences; (2) quality of psychotherapy delivered, after controlling for the severity of patients' psychopathology; (3) quality of pharmacotherapy. These variables were not entered into the analyses because we wanted to keep the predictor variables to a minimum, thus reducing the possibility of chance findings, especially in a situation where the sample size was relatively small.

There are several strengths of this study: (1) data was derived from the NIMH Treatment of Depression Collaborative Research study whose large sample size enabled us to conduct analyses of diagnostic subgroups; (2) psychotherapists were rigorously trained and monitored throughout the study; (3) treatment efficacy was partially determined by clinical evaluators who were kept blind to the treatment condition.

Chronically depressed patients have long-term maladaptive beliefs and social skill deficits (Pepper et al., 1995), which may not 'normalize' with medication alone. Studies are needed to determine if the addition of medication would significantly im-

prove social functioning and enhance their quality of life.

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