RESEARCH REPORT

Pragmatic randomized controlled trial of long-term psychoanalytic psychotherapy for treatment-resistant depression: the Tavistock Adult Depression Study (TADS)

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This pragmatic randomized controlled trial tested the effectiveness of long-term psychoanalytic psychotherapy (LTPP) as an adjunct to treatment-as-usual according to UK national guidelines (TAU), compared to TAU alone, in patients with long-standing major depression who had failed at least two different treatments and were considered to have treatment-resistant depression. Patients (N=129) were recruited from primary care and randomly allocated to the two treatment conditions. They were assessed at 6-monthly intervals during the 18 months of treatment and at 24, 30 and 42 months during follow-up. The primary outcome measure was the 17-item version of the Hamilton Depression Rating Scale (HDRS-17), with complete remission defined as a HDRS-17 score ≤8, and partial remission defined as a HDRS-17 score ≤12. Secondary outcome measures included self-reported depression as assessed by the Beck Depression Inventory - II, social functioning as evaluated by the Global Assessment of Functioning, subjective wellbeing as rated by the Clinical Outcomes in Routine Evaluation - Outcome Measure, and satisfaction with general activities as assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire. Complete remission was infrequent in both groups at the end of treatment (9.4% in the LTPP group vs. 6.5% in the control group) as well as at 42-month follow-up (14.9% vs. 4.4%). Partial remission was not significantly more likely in the LTPP than in the control group at the end of treatment (32.1% vs. 23.9%, p=0.37), but significant differences emerged during follow-up (24 months: 38.8% vs. 19.2%, p=0.03; 30 months: 34.7% vs. 12.2%, p=0.008; 42 months: 30.0% vs. 4.4%, p=0.001). Both observer-based and self-reported depression scores showed steeper declines in the LTPP group, alongside greater improvements on measures of social adjustment. These data suggest that LTPP can be useful in improving the long-term outcome of treatment-resistant depression. End-of-treatment evaluations or short follow-ups may miss the emergence of delayed therapeutic benefit.

Key words: Treatment-resistant depression, psychoanalytic psychotherapy, long-term treatment, delayed therapeutic effect

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The potential to follow a chronic, relapsing course is a substantial part of what makes depression one of the largest contributors to the burden of human disease worldwide (1,2). Treatments for major depressive disorder generally have medium effect sizes (3), but observational studies and trials consistently report high rates of non-response (4,5), with 12 to 20% of depressed patients not benefitting even from multiple courses of treatment (6). This is often termed treatment-resistant depression.

Recent systematic reviews of treatment research for this patient group, whether considered separately (7) or combined with chronic major depressive disorder (8), revealed that existing studies are mostly of poor quality and design (9). Trials of novel neuromodulation therapies – such as repetitive transcranial magnetic stimulation (10), deep brain stimulation (11) and vagus nerve stimulation (12) – with these patients have shown serious limitations. There is some evidence supporting the augmentation of initial antidepressant medication with other classes of drugs (e.g., atypical antipsychotics) (7), or the adjunct of cognitive-behavioral therapy (CBT) to that medication (8,13), at least for patients with severe but non-chronic (episode ≤2 years) major depression (14).

Evidence is accumulating that, in order to be effective, interventions for treatment-resistant depression may need to be longer and more complex than first-line treatments of depression (15), and that follow-ups should be longer (16).

Some empirical evidence for short-term psychodynamic psychotherapies in the treatment of depression is available (e.g., 17). However, given the likelihood that a longer intervention will be needed, these therapies may have little relevance to populations of patients with treatment-resistant depression (18).

Evidence-gathering regarding the effectiveness of longer-term, more intensive psychoanalytic treatments is in its early stages (19). One recent meta-analysis identified 27 studies, most being either observational or quasi-randomized, with groups matched retrospectively (20). One quasi-randomized but otherwise methodologically strong study found long-term psychodynamic psychotherapy to be less effective over the short term than brief focused therapies for a sample of mood-disordered patients. However, after a 3-year follow-up, long-term psychodynamic psychotherapy was found to be superior (21).

Notwithstanding their various methodological shortcomings, the findings of studies with a multi-year follow-up period do suggest that there may be benefits from long-term psychodynamic psychotherapy (≥50 sessions) for patients with depression (20,22), particularly in the longer term (18,23).

Given the limitations of the evidence base concerning management of treatment-resistant depression, the present pragmatic randomized controlled trial assessed whether this condition is more likely to improve when long-term psychoanalytic psychotherapy (LTPP) is provided in addition to treatment-as-usual according to UK national guidelines (TAU), but excluding the short-term forms of psychological therapy recommended by those guidelines. We hypothesized, on the basis of accumulating evidence from non-randomized controlled studies (20-22), that the effect of LTPP would increase over the course of a longer than usual follow-up period.

METHODS

Study design and participants

Patients were recruited from primary care from February 2002 to May 2009 and assessed at the Adult Service of the Tavistock & Portman National Health Service (NHS) Foundation Trust in London. They were not paid and consented only after receiving a complete written description and thorough discussion of the study.

After baseline assessment, randomization to an 18-month course of LTPP plus TAU or TAU alone was carried out offsite by an independent statistician using a stochastic minimization program (MINIM) balancing for gender, depression severity (scores of 21-39 or 40+ on the Beck Depression Inventory - II, BDI-II (24)), and medication (on/off). Patients were then followed up for 24 to 42 months post-randomization according to an intention-to-treat design.

The trial methodology was published in advance of trial completion and data analysis (25). The study protocol was registered with the International Randomized Controlled Trial Number Register (ISRCTN40586372), and approved by the Institutional Review Board of NHS West Midlands Research Ethics Committee (MREC02/07/035).

In total, 308 patients were screened for eligibility. Of these, 235 attended for interview. Inclusion criteria were: age 18-65 years; current DSM-IV diagnosis of major depressive disorder as ascertained by the Structured Clinical Interview for DSM-IV (SCID-I, 26); minimum duration of two years of the current depressive episode; minimum score of 14 on the 17-item version of the Hamilton Depression Rating Scale (HDRS-17, 27) and of 21 on the BDI-II; and at least two failed treatment attempts (elicited at interview and verified from medical records), one of which must have included treatment with an antidepressant medication, and the other with either an antidepressant medication or a psychological intervention. Exclusion criteria were: receiving psychodynamic psychotherapy in the past two years; currently, or in the past five years, meeting DSM-IV criteria for psychotic disorder or bipolar I disorder; receiving psychiatric input for substance dependence in the past two years; moderate or severe learning disability, and evidence of organic brain disorder. No assessment for presumed suitability or unsuitability for psychoanalytic forms of therapy was performed.

Treatments

LTPP consisted of 60 (50 min) sessions of once-weekly individual psychoanalytic psychotherapy over 18 months. The treatment manual (28) describes the intervention and methods, which are based on the view that depression is an outgrowth of current life difficulties arising out of painful and continuing ambivalence first felt in relation to those of the greatest emotional significance to the patient early in the course of his/her development.

The theory employed in LTPP assumes that, in patients with treatment-resistant depression, problems with psychosocial functioning impair help-seeking and illness-combating behaviors, and may also have an emotional impact upon health care/service providers in a way that affects the care they offer (29,30). LTPP enables these patients to gradually internalize a psychological capacity to relate to pathogenic personal experiences, memories, feelings, beliefs and relationships in a reflective, yet also more active, manner (31).

All the therapists (N=22; average years of experience: 17.45) had a mental health qualification and a training approved by the British Psychoanalytic Council. All therapy sessions were audio-recorded. Fidelity to treatment was assessed with the 100-item Psychotherapy Process Q-Sort (32). Three randomly selected sessions from the early, middle and end phases of each treatment were rated (183 sessions in total). Inter-rater reliability, assessed in a subsample of 90 sessions, was excellent: intraclass correlation coefficients (ICCs) after Spearman-Brown correction ranged from 0.68 to 0.98 (mean 0.87). As expected, analysis revealed that in 82.2% of cases the highest correlation obtained was with the psychodynamic prototype (mean $r=0.45$, $p<0.001$), with the remainder (17.8%) best resembling the CBT prototype (mean $r=0.28$, $p<0.05$).

TAU consisted of interventions as directed by the referring practitioner. This could include referral for other specialist provisions. In the UK's NHS, the range of these interventions is defined, and to an extent specified, in the treatment guidelines of the National Institute for Clinical Excellence (33). Referral to psychoanalytic psychotherapy is not within the guidance. In the LTPP group, the short-term forms of psychological therapy included in the guidelines were not allowed. Treatments received were recorded using the Client Service Receipt Inventory (34) and health care records.

Assessments

Assessments were based on data collected at entry; at 6, 12 and 18 months over the course of treatment; and at 24, 30 and 42 months during follow-up.

The primary outcome measure was the HDRS-17, modified to include increases in sleep, appetite and weight (35). Trained interviewers blinded to treatment condition conducted the evaluations. All evaluations were recorded, and all interviews were double-rated by an independent blinded coder to establish inter-rater reliability. An ICC of 0.89 was obtained for the total HDRS-17 score with the following severity bands: 0-7 not depressed, 8-13 mild depression, 14-18 moderate depression, 19-22 severe depression, ≥23 very severe depression. Full remission was defined as an HDRS-17 score of 8 or less (36). Following Hollon et al (14), HDRS-17 scores ≤12 were considered to meet criteria for partial remission.

Secondary outcomes included self-reported depression as assessed by BDI-II; social functioning as evaluated by the Global Assessment of Functioning (GAF, 37); subjective wellbeing as rated by the Clinical Outcomes in Routine Evaluation - Outcome Measure (CORE-OM, 38); and satisfaction with general activities as assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q, 39).

Statistical analysis

Data analysis was by intention to treat. All analyses were carried out using Stata Statistical Software Release 14 (40). Power calculations were based on statistical analysis of data from another trial of long-term psychodynamic therapy with a similarly heterogeneous population (41). We conservatively assumed an intra-cluster correlation coefficient for therapists of 0.05: with a minimum of 10 therapists delivering each therapy, each seeing on average five patients, the study with N=129 has 80% power to reject the null hypothesis of equivalence, with a non-infidelity margin equal to an effect size of 0.5 using a 95% one-sided confidence interval, on the basis of a 80% rate of follow-up to 42 months. Adequacy of randomization was assessed by between-group comparisons of baseline characteristics on all measures, using χ^2 tests for dichotomous variables and Kruskal-Wallis statistics and t-tests for count and interval data.

Treatment differences and changes over time were analyzed using the STATA ME package, which fits mixed-effects models (also known as multilevel models and hierarchical models) for a variety of distributions of the response conditional on normally distributed random effects (42). Mixed-effects models use all available data. The MIXED procedure was used for the continuous variables, including HDRS-17, BDI-II and Q-LES-Q scores. MELOGIT was used for categorical outcomes. With outcome measures that proved highly positively skewed, multilevel mixed-effects ordered probit regression (MEOPROBIT) models were applied. All model parameters for continuous outcome measures are presented here as partial standardized effects. Those for the categorical outcome measures are presented as conditional odds ratios (ORs).

The six time points of assessment were coded as −7 (baseline), −6 (6 months), −5 (12 months), −4 (18 months) of the review period, and −3 (24 months), −2 (30 months) and 0 (42 months) of the follow-up, in all models where 6-monthly data were available, thereby implying that regression coefficients involving time measured the linear rate of change from baseline to 42-month follow-up, and that regression intercepts referenced group differences at the last follow-up point. Models with random intercepts were initially fitted. Random slopes were added when likelihood ratio tests indicated a significant improvement of fit. In preliminary models, there was evidence of strong non-linear change effects in both patient groups. A quadratic time variable was therefore included in all models, but was removed if the likelihood ratio test indicated a non-significant improvement in fit.

Categorical outcome measures were best fitted by a logistic proportional odds random intercepts and slopes model. Continuous outcomes were best represented by a linear random intercepts and slopes model. Where data were seriously positively skewed, we fitted multilevel mixed-effects ordered probit regression models where the actual values taken on by the dependent variable were irrelevant, except that larger values were assumed to correspond to "higher" outcomes. As the LTPP group proved to be significantly better educated, despite random assignment to treatment groups, effects for all outcome measures were adjusted by additionally incorporating covariates for higher education into all fitted models. Adjusting for education also controlled for correlated observed asymmetries in employment and being in receipt of state (welfare) benefits.

Only those primary model parameters directly relevant to the study's objectives are presented here. These are: the overall significance of the model (Wald χ^2 statistic); modelled (intention-to-treat) group differences at 42 months (indicating whether LTPP plus TAU was better or worse than TAU alone at the last follow-up time point); the linear rate of change from baseline to 42 months for both groups combined (indicating the extent to which participants improved or deteriorated over the 3.5 years of the study); and the differential rate of change for the LTPP group (indicating whether the rate of improvement or deterioration in this group was substantially greater than in the control group).

RESULTS

Baseline characteristics

The 42 patients who, after interview, declined to participate did not differ significantly from those who accepted on any clinical variable.

Table 1 summarizes pre-treatment demographic and clinical characteristics of the 129 patients who were randomized to the two treatment conditions. The majority of these patients scored within the severe range on both HDRS-17 and BDI-II. The reported average of almost four previously

Table 1 Pre-treatment demographic and clinical characteristics of the LTPP and control groups

	LTPP group (N=67)	Control group (N=62)
Age (years, mean±SD)	42.7 ± 10.4	46.1 ± 9.9
Gender (female, %)	66.7	66.1
Currently married or cohabiting (%)	17.9	17.7
Living alone (%)	82.1	82.3
Tertiary education (%)**	59.7	35.5
Current employment (%)*	52.2	29.0
Receiving state benefits (%)**	41.8	64.5
Duration of depressive illness (years, mean±SD)	24.4 ± 11.6	19.6 ± 10.8
Duration of current episode (years, mean±SD)	3.7 ± 3.4	3.8 ± 2.6
Previously failed treatment attempts (N, mean±SD)	3.5 ± 1.4	3.9 ± 1.8
Previous suicide attempts (N, mean±SD)	0.9 ± 1.3	0.9 ± 1.3
HDRS-17 score (mean±SD)	19.8 ± 5.1	20.4 ± 4.9
HDRS-17 severe or very severe depression (%)	53.7	59.6
HDRS-17 moderate depression (%)	34.3	33.9
HDRS-17 mild depression (%)	11.9	6.5
BDI-II score (mean±SD)	36.5 ± 10.1	36.7 ± 9.5
BDI-II severe depression (score >29) (%)	74.6	77.4
Any comorbid anxiety disorder (%)	73.1	77.4
Any comorbid substance use disorder (%)	19.4	17.7
Any comorbid eating disorder (%)	16.4	9.7
Current Axis I diagnoses (N, mean±SD)	3.5 ± 1.4	3.2 ± 1.4
GAF score (mean±SD)	49.1 ± 7.0	48.8± 6.1
GAF <50 (%)	53.7	56.5
CORE global distress score (mean±SD)	22.8 ± 6.0	22.5± 6.1
CORE severe distress (score >26) (%)	44.5	40.0

LTPP – long-term psychoanalytic psychotherapy, HDRS-17 – 17-item Hamilton Depression Rating Scale, BDI-II – Beck Depression Inventory - II, GAF – Global Assessment of Functioning, CORE – Clinical Outcomes in Routine Evaluation
*p<0.02, **p<0.01

failed treatment attempts and the average GAF score <50 also highlight the considerable clinical challenge presented by this severely and chronically depressed patient group.

Patient flow is displayed in Figure 1. Attrition over four years was relatively low at 25%. Missing values were not a major problem: across all points, observations were available for 82% of primary and 75% of secondary outcome variables. There was no difference in the distribution of completer categories between the treatment groups (χ^2=1.87, df=2, p=0.18).

The two groups did not differ significantly on any pre-treatment characteristics, except that patients randomized to the LTPP group had more tertiary education (p<0.01), were more often employed (p<0.02), and received fewer state benefits (p<0.02) (see Table 1). All subsequent analyses statistically controlled for this asymmetry.

Outcomes

Complete remission (HDRS ≤8) was infrequent in both groups at the end of treatment (9.4% vs. 6.5%; χ^2=0.3; p=0.59; relative risk, RR=1.4; 95% CI: 0.3-5.8; number needed to treat, NNT=34) and at 42-month follow-up (14.9% vs. 4.4%; χ^2=2.9; p=0.09; RR=3.4; 95% CI: 0.7-15.6; NNT=9.6).

As shown in Table 2, partial remission (HDRS ≤12) was not significantly more likely in the LTPP than in the control group at the end of treatment (32.1% vs. 23.9%; χ^2=0.8; p=0.37; RR=1.3; 95% CI: 0.6-2.5; NNT=12.3), but significant differences emerged during follow-up (at 24 months: 38.8% vs. 19.2%, χ^2=4.5, p=0.03, RR=2.0, 95% CI: 1.1-4.1, NNT=5.1; at 30 months: 34.7% vs. 12.2%, χ^2=6.9, p=0.008, RR=2.8, 95% CI: 1.2-6.6, NNT=4.5; at 42 months: 30.0% vs. 4.4%, χ^2=10.3, p=0.001, RR=6.7, 95% CI: 1.6-28.3, NNT=3.9).

The odds of partial remission increased for both groups during the review period, but was 40% higher per 6-month period for the LTPP group. The difference between the estimated odds was significant at 24 months (Δ=1.1, 95% CI: 0.08-2.1, p=0.034); 30 months (Δ=1.5, 95% CI: 0.32-2.5, p=0.012); 36 months (Δ=1.8, 95% CI: 0.50-3.1, p=0.007) and 42 months (Δ=2.1, 95% CI: 0.64-3.6, p=0.005).

Mean HDRS-17 scores for all time points are displayed in Table 3. The difference between the group means became significant only at 24 months. The linear decrease in depression scores was significantly greater for the LTPP group (p<0.05). The model yielded a significant difference between groups at 42 months (p<0.01).

Using a cut-off point of 24 on the BDI-II for partial remission from moderate or severe depression, significantly more of the LTPP than the control group were in remission at 42 months (52.4% vs. 20.0%; χ^2=9.3; p=0.002; RR=2.6; 95% CI: 1.3-5.2; NNT=3.2). The mixed-effects model analysis, which predicted self-reported remission based on all observations (intention to treat) and included adjustments for covariates, confirmed the significance of the group differences at 42 months, and the decrease in the OR was significantly steeper for the LTPP group (Table 2). Modelling individual BDI-II scores showed the linear rate of decrease to be somewhat greater for the LTPP group (p<0.05). Again,

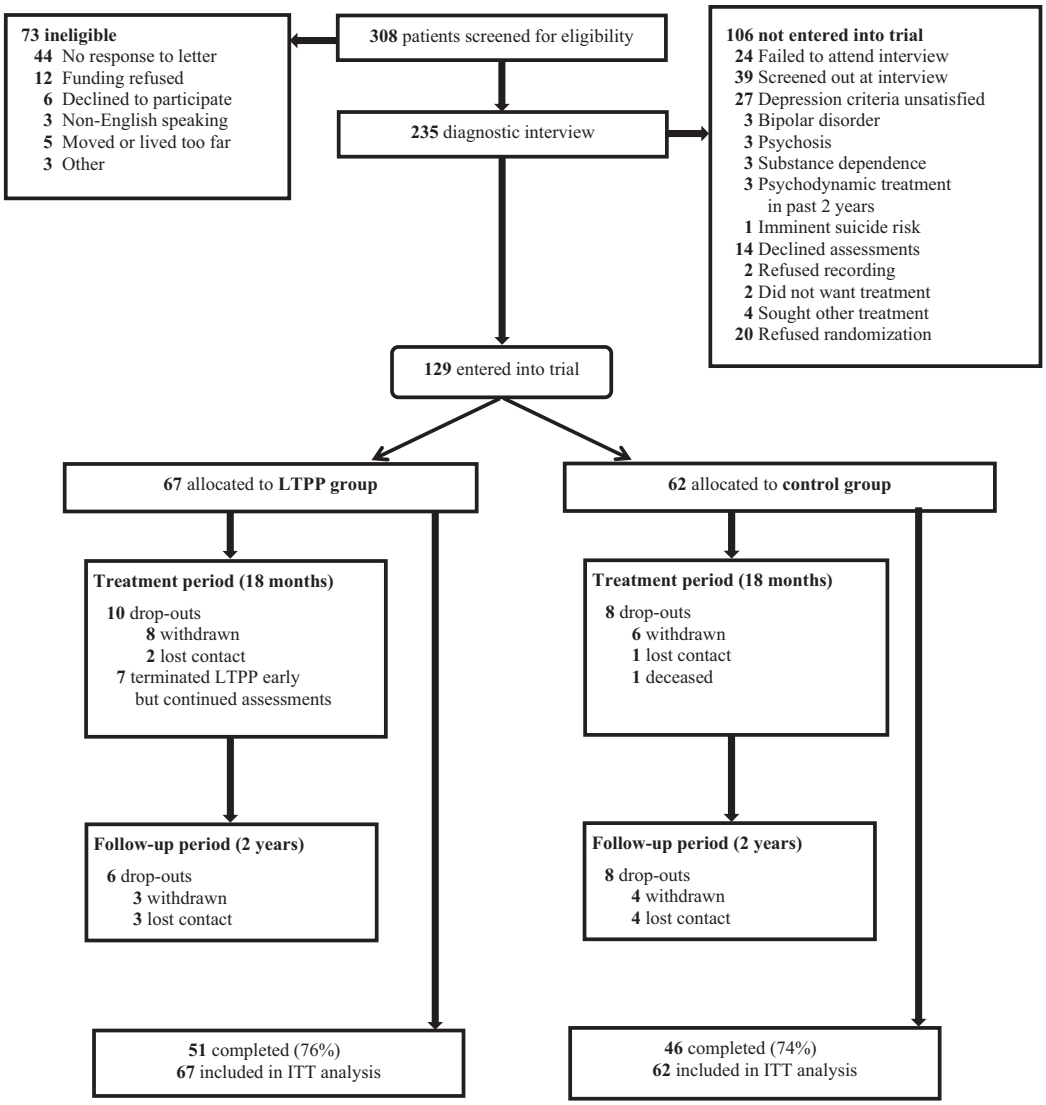

Figure 1 CONSORT diagram of patient flow through the study. LTPP – long-term psychoanalytic psychotherapy, ITT – intention to treat

the model yielded a significant difference between groups at 42 months ($p<0.05$) (Table 3). Graphical representations of these data are available from the authors upon request.

The number of participants no longer meeting DSM-IV criteria for major depressive disorder is also shown in Table 2. Mixed-effects logistic regression indicated a significant differential change in proportional ORs across the measurement points. By 42 months, 44% of the LTPP group but only 10% of the control group were in remission ($\chi^2=14.7$; $p=0.0002$; RR=4.4; 95% CI: 1.7-10.8; NNT=2.9).

Table 4 includes the mean ratings on the GAF scale. These improved for both groups over the 18-month treatment and the two years of follow-up. Improvement in the LTPP group was greater, with a highly significant observed difference at 42 months ($t=3.3$; $p=0.001$; $d=0.69$; 95% CI: 0.26-1.11). Table 4 also shows observed and modelled improvement for both groups on self-rated subjective well-being (CORE-OM) and satisfaction with general activities (Q-LES-Q), but with substantially greater benefits accruing to the LTPP group.

Treatments received

There were no significant between-group differences in the total number of prescribed medications, which increased from an average of just over two to over five in the course of the treatment; there were no significant reductions in these figures during the follow-up period (Table 5). As per protocol, the LTPP group received more psychoanalytic psychotherapy (average 41 hours, $p<0.0001$), while the control group received larger amounts of other types of psychosocial treat-

Table 2 Group differences on indicators of depression (categorical measures)

	Partial remission (HDRS-17)			Partial remission from moderate/severe depression (BDI-II)			Remission of major depression diagnosis (SCID)		
	LTPP group	Control group	χ^2	LTPP group	Control group	χ^2	LTPP group	Control group	χ^2
6 months	12/61 (19.7%)	6/56 (10.7%)	1.8	14/48 (29.2%)	11/39 (28.2%)	0.0	Not collected		
12 months	13/56 (23.2%)	11/52 (21.1%)	0.1	21/46 (45.7%)	7/40 (17.5%)	7.7**	Not collected		
18 months	17/53 (32.1%)	11/46 (23.9%)	0.8	21/45 (46.7%)	11/39 (28.2%)	3.0	20/55 (36.4%)	6/52 (11.5%)	9.0**
24 months	19/49 (38.8%)	9/47 (19.2%)	4.5*	20/41 (48.8%)	10/38 (26.3%)	4.2*	24/53 (45.3%)	8/53 (15.1%)	11.5***
30 months	17/49 (34.7%)	6/49 (12.2%)	6.9**	21/43 (48.8%)	14/41 (34.1%)	1.9	18/51 (35.3%)	7/54 (13.0%)	7.2**
42 months	14/47 (30.0%)	2/45 (4.4%)	10.3***	22/42 (52.4%)	8/40 (20.0%)	9.3**	22/50 (44.0%)	5/50 (10.0%)	14.7***
	Modelled odds ratios (95% CI)			***Modelled odds ratios (95% CI)***			***Modelled odds ratios (95% CI)***		
Model: Wald $\chi^2(df=5)$	60.2***			49.7***			39.2***		
Linear change (both groups)	4.67*** (2.84, 7.70)			2.71*** (1.80, 4.11)			4.20** (1.51, 11.40)		
Quadratic change (both groups)	0.81*** (0.76, 0.86)			0.88*** (0.83, 0.93)			0.79*** (0.70, 0.88)		
Differential linear change (LTPP)	1.41* (1.05, 1.89)			1.33* (1.05, 1.68)			2.37* (1.18, 4.84)		
Group differences at 42 months	0.09* (0.01, 0.16)			0.13* (0.01, 0.24)			0.22*** (0.09, 0.36)		

LTPP – long-term psychoanalytic psychotherapy, HDRS-17 – 17-item Hamilton Depression Rating Scale, BDI-II – Beck Depression Inventory - II, SCID – Structured Clinical Interview for DSM-IV
*p<0.05, **p<0.01, ***p<0.001

ments (average 11 hours, p<0.002), particularly counseling (27%) and CBT (19%). Patients of the control group were also significantly more likely to receive psychiatric/medical attention (37% vs. 21%).

Over follow-up, the two groups were not significantly different in terms of treatment received, although LTPP participants were slightly more likely to have received further psychodynamic psychotherapy outside the trial.

Table 3 Group differences on indicators of depression (continuous measures)

	HDRS-17 scores (mean±SD)			BDI-II scores (mean±SD)		
	LTPP group	Control group	t	LTPP group	Control group	t
Baseline (N=129)	19.8±5.1	20.2±4.8	0.6	36.5±10.1	36.7±9.5	0.2
6 months (N=117)	16.8±6.0	18.3±5.8	1.4	29.9±12.4	32.6±15.3	0.9
12 months (N=108)	17.1±6.1	17.9±6.3	0.6	27.4±14.5	34.7±13.4	2.4**
18 months (N=99)	16.4±6.2	17.9±6.5	1.1	28.0±12.8	34.3±16.6	2.1*
24 months (N=96)	15.4±6.6	17.6±6.1	1.7*	25.9±16.4	34.1±16.1	2.3**
30 months (N=98)	16.7±7.4	19.4±6.5	1.9*	27.0±16.0	31.0±15.8	1.3
42 months (N=92)	15.9±6.8	20.1±5.4	3.2***	24.0±14.4	34.5±14.2	3.3***
	Adjusted model coefficients (95% CI)			***Adjusted model coefficients (95% CI)***		
Model: Wald $\chi^2(df=5)$	53.3***			44.4***		
Linear change (both groups)	−1.20*** (−1.64, −0.74)			−2.22*** (−3.26, −1.17)		
Quadratic change (both groups)	0.17*** (0.11, 0.22)			0.28*** (0.14, 0.42)		
Differential linear change (LTPP)	−0.36** (−0.64, −0.07)			−0.84* (−1.57, −0.12)		
Group differences at 42 months	−2.71** (−5.16, −0.29)			−6.94* (−12.87, −1.00)		

LTPP – long-term psychoanalytic psychotherapy, HDRS-17 – 17-item Hamilton Depression Rating Scale, BDI-II – Beck Depression Inventory-II
*p<0.05, **p<0.01, ***p<0.001

Table 4 Group differences in measures of social functioning, subjective wellbeing and satisfaction with general activities

	GAF scores (mean±SD)			Subjective wellbeing, CORE-OM (mean±SD)			Satisfaction with general activities, Q-LES-SQ (mean±SD)		
	LTPP group	Control group	t	LTPP group	Control group	t	LTPP group	Control group	t
Baseline (N=129)	49.1±7.1	48.8±6.1	0.2	2.4±0.6	2.3±0.6	0.8	28.9±14.7	29.2±15.1	0.1
6 months (N=115)	Not collected			2.2±0.7	2.2±0.8	0.2	36.3±15.8	35.3±17.5	0.3
12 months (N=106)	Not collected			2.2±0.7	2.3±0.7	0.7	37.1±15.2	35.2±16.8	0.6
18 months (N=96)	57.3±9.8	52.5±9.2	2.4**	2.0±0.7	2.3±0.8	1.8*	38.8±18.0	32.6±19.9	1.5
24 months (N=94)	60.1±9.7	54.3±9.2	3.0**	1.9±0.8	2.2±0.8	1.6*	43.1±21.2	30.9±21.0	2.5**
30 months (N=95)	58.6±12.5	52.6±11.9	2.4**	1.9±0.8	2.1±0.9	0.7	41.7±20.1	35.3±22.0	1.4
42 months (N=91)	60.0±12.9	52.4±8.1	3.3***	1.8±0.8	2.3±0.7	2.9**	45.6±19.9	32.0±19.0	3.1***
	Adjusted model coefficients (95% CI)			*Adjusted model coefficients (95% CI)*			*Adjusted model coefficients (95% CI)*		
Model: Wald $\chi^2(df=5)$	98.0***			29.3***			40.1***		
Linear change (both groups)	2.29*** (1.53, 3.05)			−0.08** (−0.14, −0.02)			2.12** (0.62, 3.62)		
Quadratic change (both groups)	−0.25*** (−0.34,−0.15)			0.01** (0.00, 0.02)			−0.29** (−0.48,−0.10)		
Differential linear change (LTPP)	0.81** (0.24, 1.38)			−0.06** (−0.10,−0.01)			1.75*** (0.67, 2.82)		
Group differences at 42 months	6.01** (1.80, 10.22)			−0.32* (−0.64, −0.00)			10.33** (2.46, 18.21)		

LTPP – long-term psychoanalytic psychotherapy, GAF – Global Assessment of Functioning, CORE-OM – Clinical Outcomes in Routine Evaluation - Outcome Measure, Q-LES-SQ – Quality of Life Enjoyment and Satisfaction Questionnaire
*p<0.05, **p<0.01, ***p<0.001

DISCUSSION

This is the first fully randomized controlled trial of a manualized LTPP for treatment-resistant depression. Improvements in depression were modest but comparable between the LTPP and the control group until termination of treatment, while differences emerged from 24 months post-randomization, with the LTPP group mostly maintaining the gains achieved while the control group appeared to be at greater risk of relapse. At 2-year follow-up, almost one-third of the participants receiving LTPP were still in partial remission, compared with only 4% of those in the control group. At that time, 44% of the LTPP group no longer met diagnostic criteria for major depressive disorder, compared with 10% of those receiving TAU alone.

The effect sizes observed are in the medium range. The long-term outcomes of LTPP compare favorably with effect sizes reported in comprehensive reviews (3), including those used by the UK treatment recommendations (33). Studies that show stronger effects tend to observe patients in whom treatment resistance is less evident and lack information about long-term outcomes (43). Further comparisons, including longer manualized treatments based upon other (non-psychoanalytic) psychological therapy modalities such as CBT, are needed to establish the specificity of the therapeutic gain reported here.

As predicted, differences between the LTPP and the control group increased during follow-up on most measures. A Finnish longitudinal study of LTPP has reported a similar pattern with a less chronically depressed patient group (44), suggesting that LTPP may require some time post-treatment for its full effects to become evident (45). End-of-treatment evaluations or follow-ups that are too short may miss the emergence of this delayed therapeutic benefit.

While this study has ecological validity in that it employed a relatively unselected sample and incorporated a comparatively long follow-up, it has several limitations. First, the design of the study did not allow masking of patients to the treatment allocation, which may have generated an expectation bias. Second, although mixed-effects models are thought to be robust even to selective loss of data (46), we still failed to collect primary outcome data for over 25% of patients at 42 months, despite an unusually good level of retention for patients with depression of this severity. Third, the differences between the effects associated with the two treatments could have arisen as a result of the disparities between their respective numbers of contact hours, intensity, and quality of case management (47). Fourth, in spite of robust procedures, randomization yielded a difference between groups in education level, with associated asymmetries in employment and state benefits, which we were forced to adjust for statistically. Reanalysis in which the samples were balanced by selectively excluding patients did not alter the basic pattern of findings. Fifth, while we were concerned to measure outcome over an extended period, we omitted to include an interval depression measure such as the Longitudinal Interval Follow-up Evaluation (48). Sixth, since the study was planned and conducted by the developers of the inter-

Table 5 Treatments delivered to patients of LTPP and control groups in periods before randomization (6 months), during treatment (18 months) and during follow-up (24 months)

	Period before randomization			Treatment period			Follow-up period		
	LTPP group	Control group	t or χ^2	LTPP group	Control group	t or χ^2	LTPP group	Control group	t or χ^2
Medications									
Antidepressants (%)	82.0	80.7	<1	85.0	79.0	<1	79.0	74.2	<1
Anxiolytics/hypnotics (%)	41.8	45.2	<1	40.3	41.9	<1	34.3	35.5	<1
Antipsychotics/ mood stabilizers (%)	9.0	3.2	<1	11.9	11.3	<1	13.4	16.1	<1
Analgesics (%)	37.3	40.3	<1	35.8	41.9	<1	29.9	41.9	χ^2=2.05
Other medications (%)	23.9	30.6	<1	23.9	33.9	χ^2=1.57	28.4	37.1	χ^2=1.12
No medication (%)	9.0	6.5	<1	7.5	6.4	<1	15.0	9.7	<1
Number of medications (mean±SD)	2.1 ± 1.4	2.0 ± 1.2	<1	5.0 ± 4.2	5.3 ± 3.9	<1	4.6 ± 4.4	5.2 ± 4.1	<1
Psychosocial treatments									
Psychodynamic psychotherapy (hours, mean±SD)	0.8 ± 6.3	0	<1	41.4 ± 21.4	0.4 ± 3.0	t=15.0***	3.6 ± 11.0	0.8 ± 6.6	t=1.7
Other therapies (hours, mean±SD)	6.2 ± 11.3	7.7 ± 14.7	<1	3.2 ± 11.6	11.2 ± 18.4	t=2.98***	6.2 ± 11.5	8.1 ± 16.2	<1
CBT (%)	9.0	8.1	<1	1.5	19.4	χ^2=11.4***	10.5	8.1	<1
Counseling (%)	37.3	42.0	<1	1.5	27.4	χ^2=18.1***	16.4	17.7	<1
Clinical psychologist (%)	22.4	17.7	<1	11.9	14.5	<1	13.4	11.3	<1
Psychotherapist (%)	12.0	13.0	<1	7.5	11.2	χ^2=2.4	16.4	23.6	χ^2=2.5
Other interventions									
Psychiatric/medical (hours, mean±SD)	2.3 ± 5.2	0.5 ± 1.9	t=2.56**	1.3 ± 3.7	1.5 ± 3.1	<1	1.2 ± 3.5	1.8 ± 6.1	<1
Psychiatric/medical (%)	31.3	16.1	χ^2=4.1*	20.9	37.1	χ^2=4.1*	22.4	27.4	<1
Social worker/OT/nurse (%)	9.0	9.7	<1	9.0	9.7	<1	7.5	6.5	<1
Self-help groups (%)	4.5	4.8	<1	4.5	4.8	<1	4.5	4.8	<1
Day centre (%)	0	0	<1	1.5	1.6	<1	1.5	0	<1
Hospital admissions (%)	4.0	0	χ^2=3.82	3.0	1.6	<1	4.5	4.9	<1

LTPP – long-term psychoanalytic psychotherapy, CBT – cognitive-behavioral therapy, OT – occupational therapy
*p<0.05, **p<0.01, ***p<0.001

vention, there is a risk of allegiance bias (49). We tried to minimize this risk by having the primary outcome measure assessments made by interviewers who were blinded to the treatment condition. Seventh, these results were delivered by a single provider organization. This may limit generalizability. However, a multi-center German trial (the LAC Study) (50), testing LTPP using the same manual with a similar patient group, will shortly report.

In conclusion, while the benefit of both interventions for this severely affected group of patients with major depressive disorder was limited, a moderate difference emerged over long-term follow-up in favor of the LTPP condition. Further studies are needed to replicate this finding, ascertain its clinical utility, understand the mechanisms involved, and identify factors associated with response or non-response to treatment.

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