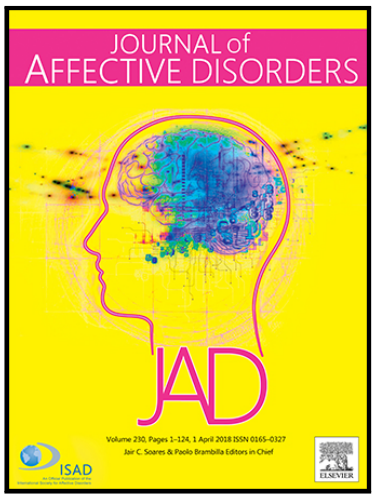

Article:
Town, J.M., Abbass, A., Stride, C. et al. (2020) Efficacy and cost-effectiveness of intensive short-term dynamic psychotherapy for treatment resistant depression: 18-month follow-up of the Halifax depression trial. Journal of Affective Disorders, 273. pp. 194-202. ISSN: 0165-0327

https://doi.org/10.1016/j.jad.2020.04.035



Efficacy and Cost-Effectiveness of Intensive Short-Term Dynamic Psychotherapy for Treatment Resistant Depression: 18-Month Follow-Up of The Halifax Depression Trial

Joel M. Town , Allan Abbass , Chris Stride , Abraham Nunes , Denise Bernier , Patrick Berrigan

PII: S0165-0327(20)30841-7
DOI: https://doi.org/10.1016/j.jad.2020.04.035
Reference: JAD 11902

To appear in: *Journal of Affective Disorders*

Received date: 9 March 2020
Revised date: 1 April 2020
Accepted date: 24 April 2020

Please cite this article as: Joel M. Town , Allan Abbass , Chris Stride , Abraham Nunes , Denise Bernier , Patrick Berrigan , Efficacy and Cost-Effectiveness of Intensive Short-Term Dynamic Psychotherapy for Treatment Resistant Depression: 18-Month Follow-Up of The Halifax Depression Trial, *Journal of Affective Disorders* (2020), doi: https://doi.org/10.1016/j.jad.2020.04.035

Highlights

- This RCT at 18-month follow-up found that ISTDP showed sustained treatment gains for TRD.
- At 18 months follow-up 40% of ISTDP patients were in remission from depression.
- Health economic analysis suggests that ISTDP is a cost-effective treatment for TRD compared to routine treatment provided in secondary care mental health teams.

Efficacy and Cost-Effectiveness of Intensive Short-Term Dynamic Psychotherapy for Treatment Resistant Depression: 18-Month Follow-Up of The Halifax Depression Trial

Joel M. Town[1], Allan Abbass [2], Chris Stride[3], Abraham Nunes[4], Denise Bernier[5], Patrick Berrigan[6]

[1]DClinPsy, Assistant Professor Department of Psychiatry, Dalhousie University, Halifax, Canada.

[2]MD, FRCPC, Professor Department of Psychiatry, Dalhousie University, Halifax, Canada.

[3]PhD, Senior Lecturer/Statistician, The Institute of Work Psychology, University of Sheffield, Sheffield, UK.

[4]MD, MBA, Department of Psychiatry & Faculty of Computer Science, Dalhousie University, Halifax, Canada.

[5]PhD, Assistant Professor Department of Psychiatry, Dalhousie University, Halifax, Canada.

[6]MA, Research Consultant, Research Methods Unit, Nova Scotia Health Authority, Halifax, Canada.

Correspondence concerning this article should be addressed to Dr. Joel Town, Abbie J. Lane Bldg, 7th Floor, Rm 7507, 5909 Veteran's Memorial Lane, Halifax, Nova Scotia, B3H 2N1. Phone: 902-473-2543, Fax: 902-473-1422, Email: joel.town@dal.ca

Abstract

Background

Depressed patients with chronic and complex health issues commonly relapse; therefore, examining longer-term outcomes is an important consideration. For treatment resistant depression (TRD), the post-treatment efficacy of time-limited Intensive Short-Term Dynamic Psychotherapy (ISTDP) has been demonstrated but longer-term outcomes and cost-effectiveness are unclear.

Method

In this superiority trial, 60 patients referred to Community Mental Health Teams (CMHT) were randomised to 2 groups (ISTDP=30 and CMHT=30). The primary outcome was Hamilton Depression Rating scale (HAM-D) scores at 18 months. Secondary outcomes included Patient Health Questionnaire (PHQ-9) depression scores and dichotomous measure *remission*. A health economic evaluation examined mental health costs with quality-adjusted life years (QALYs).

Results

Statistically significant treatment differences in depression previously found at 6 months favouring ISTDP were maintained at 18-month follow-up. Group differences in depression were in the moderate to large range on both the observer rated (Cohen's *d* = .64) and self-report measures (Cohen's *d* = .70). At 18 months follow-up the remission rate in ISTDP patients was 40.0%, and 23.4% had discontinued antidepressants. Health economic analysis suggests that ISTDP was more cost-effective than CMHT at 18 months. Probabilistic analysis suggests that there is a 64.5% probability of ISTDP being cost-effective at a willingness to pay for a QALY of $25,000 compared to CMHT at 18 months.

Limitations

Replication of these findings is necessary in larger samples and future cost analyses should also consider indirect costs.

Conclusions

ISTDP demonstrates long-term efficacy and cost-effectiveness in TRD.

Declaration of Interests

None

Key words: Treatment resistant, Depression, Psychodynamic Psychotherapy, Randomised trial, Cost effectiveness

1. Introduction

Depression is amongst the largest single causes of disability worldwide, and the disease burden of depression is on the rise globally (Murray and Lopez, 1997; WHO, 2013). Antidepressant treatment is considered a first line agent for major depression. However, up to half of patients do not show a satisfactory response (Kubitz et al., 2013). With every failed treatment the patient's long-term prognosis deteriorates (Rush et al., 2006). Where adequate treatment dose and duration were applied, such cases are termed treatment resistant depression (TRD). A more specific indication for degree of treatment resistance may be based upon the number and type of prior antidepressant medication failures (Fava, 2003) and psychotherapy

treatments that did not lead to symptom remission.

A 2011 review of psychotherapy treatment for TRD found only 6 trials (Trivedi et al., 2011). Subsequent randomised controlled trials (RCTs) have reported mixed findings (Eisendrath et al., 2016; Fonagy et al., 2015; Souza et al., 2016; Wiles et al., 2013). We recently reported an RCT showing that Intensive Short-Term Dynamic Psychotherapy (ISTDP) is efficacious in the treatment of TRD (Town et al., 2017). ISTDP showed statistically significant improvements in depressive symptoms, in the moderate to large range, compared to routine treatment by secondary care Community Mental Health Teams (CMHTs): after 6 months patients in the ISTDP group were more likely to achieve complete remission (36.0% vs. 3.7%) or partial remission (48.0% vs. 18.5%).

Alongside the paucity of empirical support for psychotherapies with TRD, there is a shortage of information on longer-term outcomes, though relapse and reoccurrence rates are typically high. At 24 months after treatment for TRD, patients randomly allocated to long-term psychoanalytic psychotherapy demonstrated sustained benefit (Fonagy et al., 2015). Cognitive behaviour therapy (CBT) also showed significant advantages at a 40-month follow-up in TRD (Wiles et al., 2016). Complete remission rates in these TRD RCTs at long-term follow-up for the psychotherapy treatments were just 14.9% and 28% respectively.

In this study, we examined whether the effects of ISTDP are sustained 12 months after treatment, compared with patients receiving ongoing treatment at CMHTs. In our earlier study, short-term outcomes in the ISTDP group revealed significant improvement in depressive symptoms, declining from severe at baseline to mild/moderate at end of treatment. Meta-analyses of long-term outcomes of Short-Term Psychodynamic Psychotherapy (STPP) report sustained treatment effects in follow-up, and indicate further small improvement (Driessen et al., 2015). With complex, refractory, often chronic depression, evidence from previous trials suggests that further post-treatment gains in TRD are unlikely. We therefore hypothesized that the decrease in ISTDP patients' depression during the course of treatment would flatten off and stabilize after treatment ended, but the treatment gains observed would remain greater in patients who received ISTDP compared to CMHT treatment. Finally, we examined cost-effectiveness of ISTDP versus CMHT treatment.

2. Methods

2.1. *Study Design*

This superiority trial used a single blind randomised parallel group design to examine the efficacy of ISTDP versus secondary care treatment as usual (TAU) provided by CMHTs, for depressed patients who were non-remitting following at least one antidepressant treatment course. The original study design and power calculation, that resulted in the recruitment of 60 participants, has previously been described (Town et al., 2017).

The primary cost-effectiveness analysis (CEA) assesses the value for money of ISTDP versus CMHT in terms of the incremental cost required to gain incremental improvement in quality adjusted life years (QALYs) over the 18-month study period. A secondary CEA was conducted to assess the value for money of intensive ISTDP versus CMHT in terms of the incremental cost required to gain incremental improvement in the HAM-D over the 18-month study period. In both the primary and secondary analyses, cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs). The present study takes the cost perspective of the mental health payer and measures cost in 2017 Canadian Dollars. For a detailed description of the CEA see the Online Appendix.

The study protocol was registered with ClinicalTrials.gov (ID: NCT01141426) and approved by the Nova Scotia Health Authority Research Ethics Board (NSHA-RS/2013-049). All participants provided written informed consent.

2.2.Participant Eligibility and Recruitment

Between September 2012 and March 2015, 143 potential participants were referred to the study by clinicians from 4 secondary care outpatient CMHTs based in Halifax Regional Municipality, Nova Scotia, Canada. Patients eligible to be referred were outpatients, aged 18-65 years, with a primary diagnosis of major depressive disorder according to DSM-IV criteria. Patients met study criteria for TRD by having had at least one trial of antidepressants at the adequate recommended therapeutic dose; a current depressive episode duration of 6 or more weeks; inadequate response to treatment (assessed by 17-item HAM-D score ≥ 16); not having started further medication or changed dose of existing medication in the previous 6 weeks; and not having received treatment in the previous 2 years at any of the 4 CMHTs. Of the 120 patients assessed, 60 did not meet inclusion criteria or declined participation, hence were excluded. The study's CONSORT diagram is presented in Figure 1.

2.3.Randomisation and Allocation

Research assistants, who remained blind throughout the randomisation and allocation process, conducted screening assessments and enrollment. At the end of enrollment, an administrator allocated patients to ISTDP or CMHT treatment in a 1:1 ratio. For purposes of randomisation a researcher external to the study team generated a permuted block randomisation sequence using a random number generator.

2.4.Intervention Protocol

2.4.1. Intensive Short-Term Dynamic Psychotherapy

The ISTDP treatment provided is discussed in detail in our earlier study (Town et al., 2017). ISTDP was delivered in a 20-session time-limited, individual format, and according to published recommendations (Abbass, 2015; Davanloo, 2000). The mean number of sessions completed was 16.1 (SD = 6.68) (Town et al., 2017). ISTDP therapists were licensed professionals with supervised experience practicing ISTDP (mean experience = 10.25 years, range = 4-20 years). Trained independent researchers established the integrity of the ISTDP intervention (Town et al., 2017) using the Comparative Psychotherapy Process Scale (CPPS) (Hilsenroth et al., 2005).

2.4.2. Medication Management

A medication washout phase was not specified in the protocol prior to treatment allocation to avoid possible withdrawal and subsequent treatment effects. For participants receiving ISTDP it was requested that medication(s) remain stable. Participants' general practitioners (GP) were contacted to monitor medication. Participants were advised to discuss medication with their GP. For participants receiving care at a CMHT, pharmacotherapy treatment strategies consisted of individualized regimes informed by Canadian-based clinical guidelines (Lam et al., 2009).

2.4.3. Secondary Care Treatment at Community Mental Health Teams

At each CMHT site, treatment consisted of a multidisciplinary team including pharmacotherapy and clinical management, supportive or structured activities focused around symptom management and, in some cases, individual or group psychotherapy. Treatment was unregulated, thus facilitating a naturalistic assessment of standard secondary care treatment- except that the trial CMHT participants were not offered ISTDP. Patients receiving CMHT treatment could receive ongoing care beyond the 6-month assessment. Due to the range of interventions available, formal treatment integrity ratings were not conducted, but details on doses, duration, and approaches delivered were documented. In our previous study, we reported that in

the CMHT group during the initial 6-month study period, 29 participants (97%) received at least one session of talking therapy (mean number of sessions = 7.6, SD = 3.7). The one-to-one therapy delivered by CMHTs was primarily counseling (57%) or CBT (40%). In addition, 15 participants (50%) received group therapy within a structured 10-12 two-hour session CBT format. Participants receiving CMHT treatment were more likely to have pharmacotherapy increased or changed than those in the ISTDP group (53% vs. 10%).

2.5. Outcome Measures

We conducted outcome assessments at study baseline, mid-treatment (pre-session 11), post-treatment, and then 3, 6 and 12 months post-treatment in the ISTDP group. CMHT group patients followed an equivalent assessment schedule, specifically at the study baseline and then at 3, 6, 9, 12 and 18 months following enrolment.

2.5.1. Primary Outcome

The primary measure of participants' depressive symptomology was the observer-rated 17-item HAM-D (Hamilton, 1967). A research assistant was trained to use a standardized clinical interview to administer this structured rating system designed to assess depressive symptom severity (Bech et al., 2003). During training, 3 clinical interviews were rated by the evaluator and ratings compared with an expert's ratings. Research assistants were blind to treatment condition. Patients were instructed to refrain from discussing their treatment during assessments. All interviews were videotaped to assess rating reliability. To prevent rater drift the evaluator met with an independent experienced evaluator (clinical psychologist) at regular intervals to review videotaped interviews. Twenty-six HAM-D assessments were independently rated by both evaluators. The average between-rater intraclass correlation coefficient, ICC (2,1), was 0.96.

2.5.2. Secondary Outcomes

Our secondary depression outcome was the scale sum score from the 9-item patient-rated Patient Health Questionnaire (PHQ-9) (Kroenke and Spitzer, 2002). Additional secondary outcome measures included self-reported anxiety measured using the Generalized Anxiety Disorder scale (GAD-7) (Spitzer et al., 2006); psychological well-being rated with Clinical Outcomes in Routine Evaluation Outcome Measure (CORE-OM: overall score) (Barkham et al., 2005); interpersonal functioning via the Inventory of Interpersonal Problems (IIP-32: overall score) (Horowitz et al., 2000); and somatic symptoms were measured (Patient Health Questionnaire PHQ-15) (Kroenke et al., 2001).

For a series of supplementary descriptive analyses, we converted the sum score versions of the HAM-D and PHQ-9 to binary outcomes representing full and partial remission. 'Being in remission' was defined as achieving a HAM-D score ≤ 7; 'response', by the HAM-D score having reduced by ≥ 50% from baseline. For the PHQ-9 measure, remission was defined as achieving a scale sum of ≤ 4; 'response' by a reduction of ≥ 50%.

2.5.3. Measuring Cost Effectiveness

The CEA used QALYs calculated with the SF-6D scoring algorithm using data collected with the SF-12 (Ware et al., 1996); and also HAM-D scores. Costs included in the analysis are: interventional costs (ISTDP and CMHT); inpatient costs; outpatient costs; physician fees; out-of-pocket costs; and medications related to mental health. Service utilization was identified using a combination of medical chart review, patient self-report using the Trimbos and Institute of Medical technology Assessment Cost Questionnaire for Psychiatry (TIC-P) (Hakkaart-van Roijen, 2002) at each follow-up period, and the study jurisdiction's administrative database for physician billings. Data related to indirect time delivering ISTDP treatment, including preparation and supervision, was collected from study therapists. The costs described above were calculated by multiplying estimates of the unit prices by the number of times the corresponding service was used, with the exception of physician billings, which were obtained from a jurisdictional database. Additional costing information is provided in the Supplementary Appendix.

2.6.Statistical Analyses

Within psychotherapy research, models for longitudinal data have typically been restricted to linear change, i.e.,

$$y = b0 + b1*time$$

However, change rarely continues linearly in perpetuity. Curvilinearity is sometimes modelled via adding a quadratic term to a linear model, i.e.

$$y = b0 + b1*time + b2*time^2$$

but under this model our predicted value will still eventually accelerate towards plus or minus infinity as time increases.

The most appropriate way to model decelerating change towards a limit or 'asymptote' is by a 'true' non-linear function, typically an 'exponential decay' model of the form,

$$y = asymp + (init - asymp)*exp(-1*rate*time)$$

where *time* is coded from the start of the study (i.e. time-point 1 is *time* = 0) and the parameters (regression coefficients) estimated represent the initial level (i.e. intercept) of depressive symptoms (*init*); the asymptote (*asymp*); and the shape of change (*rate*). This true non-linear function approach is recommended (Pinheiro and Bates, 2001; Singer and Willett, 2003) when the underpinning theoretical model involves convergence to a stable level, known as an 'asymptote', as opposed to continuous linear decrease or increase. We re-parameterised this model to contain a parameter *diff*, where diff represented, and hence provided a test of the difference between the initial (time 1) value of the outcome and the asymptote (the level at which it had stabilized), i.e., the model we fitted for each outcome was

$$y = (init - diff) + diff*exp(-1*rate*time)$$

where

$$diff = init - asymp$$

Given the multilevel nature of our data (six observations over time nested within patients, giving us non-independence of observations), we treated the intercept (in the non-linear context, parameter *init)* as a random effect. For each outcome we first calculated an unconditional model (no predictors) to give baseline estimates for within- and between-subject variance. We then compared the non-linear exponential decay model outlined above with the more ubiquitous linear and quadratic models. Where the non-linear model was best, we added random effects, for *diff* and *rate*, with these variance term(s) retained if they enhanced model fit. Finally, we aimed to explain any variation in *init*, *diff* and/or *rate* by treatment group membership: if the extent and shape of change varied between patients, was this due to different treatment (i.e., ISTDP or CMHT) received?

Models were fitted using the linear and non-linear mixed effects packages (lme, nlme) in open-source statistical programming software R. In each model we included an autoregressive (AR1) random effect to

account for the within-subject correlation structure of repeated measures data. Time was coded in units of '3 months from the start of the study' (time point 1 = 0, time point 2 = 1, etc). Non-linear models were compared with the linear options by the (smaller is better) Akaike and Bayesian Information Criteria (AIC and BIC). Non-linear models with differing random effects were compared using a chi-square difference test. The $p < 0.05$ level of statistical significance was used throughout.

For each outcome we also calculated effect sizes (Cohen's *d*) for change between time points 1 and 6, by group, using the estimated marginal means from the best model for each outcome, and sample standard deviations.

2.7.Cost-effectiveness Analysis

Differences between groups in non-discounted service use costs over the 18-month trial period were examined using t-tests and costs were log-transformed to account for skewness.

In the primary analysis, ISTDP was compared to CMHT using QALY's and secondary analysis used HAM-D scores. We used multiple predictive imputation (MI) to address missing data for the SF-6D. Predictor variables included in the MI were those shown to be significantly correlated with quality of life: age, gender, marital status, employment status, education, and length of unemployment. We performed the analysis on 10 imputed datasets, and the results combined using Rubin's rule (Rubin, 1987).

ICER in the reference case analysis were calculated using the difference in cost and difference in QALY between groups over the 18-month trial, discounted at 1.5%. A cost effectiveness acceptability curve (CEAC) illustrating the probability of the intervention being effective at different willingness-to-pay threshold values was produced. ICER in the secondary analysis were calculated using the difference in cost and the difference in improvement in HAM-D scores between groups over the 18-month trial. Cost data were discounted at 1.5% and HAM-D scores were not discounted.

Sensitivity analyses were performed to assess the results of CEA. Additional ICER were calculated using discount rates of 0% and 3%. Further sensitivity analyses were also conducted using QALY calculated using mean interpolation to address missing data instead of the MI approach. Further sensitivity analysis is conducted removing high volume service users. A probabilistic analysis (PA) is also conducted for both the primary and secondary CEA. Additional details for and results of the sensitivity analyses are reported in the Online Appendix.

2.8.Adverse Events

Adverse events during the trial's initial 6 months occurred in two participants in the CMHT group who reported increases in depressive symptoms (Town et al., 2017). In the 12 months follow-up, due to a deterioration in mental health, one participant from each treatment condition required mental health inpatient care. Neither patients' decline in mental health was judged to be related to the study intervention.

3. Results

3.1. *Sample Description*

As reported within our previous study (Town et al., 2017), no significant differences were found in participant clinical characteristics between the treatment conditions. The majority of participants scored within the severe range on the HAM-D alongside comorbid mental health disorders and chronic physical illness; 96.7% had a comorbid Axis I disorder; 89.7% fulfilled criteria for Axis II personality disorder. The 60 randomised participants were included in our primary 'intention to treat' analysis sample. Of the 30 participants randomised to ISTDP, 2 dropped out of the study immediately after randomisation due to work commitments; 1 dropped out after 1 session, and 2 more dropped out after 8 sessions, again due to work commitments. In the CMHT group, all participants were seen for at least one appointment. Figure 1 summarises participant flow through the study.

The aforementioned treatment drop-out was accompanied by a handful of non-completed measures at time points 1 to 3, and a larger degree of non-response at latter time points. Our primary intention to treat analysis included all available patient data. This final sample consisted of 279 responses from 60 participants, with complete data at time-point 1 (baseline), 55 participants responding at time-point 2, 52 at time-point 3, 39 at time-point 4, and 37 at time-point 5 and 6. Thirty-six participants (17 receiving CMHT treatment, 19 receiving ISTDP) responded at all time points.

3.2.Treatments Received

During the 12-month follow-up assessment period, data were collected on treatments received for 58 of the randomised participants (ISTDP = 30; CMHT = 28). Table 1 summarises the treatment received within the experimental and comparison conditions. Participants in the CMHT group were more likely to receive talking therapy, participate in group CBT, and receive psychosocial interventions than those in the ISTDP group. Pharmacotherapy utilization was lower in the follow-up period for the ISTDP group:

participants were less likely to receive antidepressants or have psychiatric medications changed and more likely to be medication free at 18 months. Across the study period there was a significant reduction in the total number of psychiatric medications prescribed in the ISTDP group but a significant increase in psychiatric medications prescribed within the CMHT group.

3.3.Modelling Continuous Outcomes

Model comparisons and random effects estimates for HAM-D and PHQ-9 are given in the Online Appendix, with fixed coefficients from the final (best) model for each outcome presented in Table 2. Equivalent statistics for secondary outcomes (GAD-7, IIP-32, CORE-OM, and PHQ-15) are given in the Online Appendix.

For all outcomes other than IIP (linear change), the exponential decay model outperformed linear or quadratic models. Estimated growth curves for outcomes modelled using an exponential decay model have converged very close to their asymptote after 3 time points, i.e. at the end of treatment, and offer a good fit to the sample means (see Figure 2). Basic effect sizes (Cohen's *d*) for group differences at each time point are given for HAM-D and PHQ-9 in Table 3.

For the primary outcomes HAM-D and PHQ-9, adding a random effect for the difference parameter improved model fit (change in -2LL = 11.851, 1df, $p < 0.05$; change in -2LL = 8.552, 1df, $p < 0.05$, $p < 0.05$ respectively), but there was no evidence for variation between subjects in the rate of symptom decrease.

Treatment group was unrelated to the initial (intercept) level of all outcomes (as would be expected given the randomised group allocation). Treatment group was, however, a significant predictor of the difference parameter for both HAM-D and PHQ-9. The ISTDP group reported a greater decrease in depressive symptoms from time 1 to the asymptote ($B = 4.184$, $p < 0.05$; $B = 4.082$, $p < 0.05$ respectively). Treatment group explained 9.5% of between-subject variance in the decrease for HAM-D, and 11.3% of variance in the decrease for PHQ-9. Treatment group was unrelated to the difference parameter for the other secondary outcomes.

These results support our primary hypothesis that ISTDP yields a greater improvement in patients' depressive symptoms relative to CMHT treatment at the 18-month study period. More specifically, the degree of treatment gains observed after 6 months remained greater in patients who received ISTDP and stabilized over the next year (Figure 2).

3.4.Percentage Remission

The proportion of cases in full remission and showing response follow the pattern displayed by continuous versions of the measures, namely an improvement during treatment followed by stabilization in the 12 months follow-up. Comparing the ISTDP group to CMHT, HAM-D full remission stabilizes at approximately 40% vs. 29%; response, at 50% vs. 41%. PHQ-9 full remission stabilizes at approximately 30% vs. 25%; response, at 55% vs. 38%.

3.5.Cost Effectiveness

Over the total 18 months of the trial, the log-transformed non-discounted total cost for the CMHT group was slightly lower than that for the ISTDP group, but the difference in between groups was not statistically significant. The mean difference in log- transformed costs was -0.04 (95% CI = -0.36 to 0.28, p = 0.81). When using the raw rather than log-transformed scores, the direction of this difference was reversed: this is the result of several high-volume service users within the CMHT group.

Using total healthcare costs and QALYs as the measure of effect, the ISTDP group offered lower cost and higher quality of life (0.90 vs 0.87) at 18 months with a discount rate of 1.5% (See Table 4). Alternative discount rates of 0% and 3% did not substantially affect findings. In the secondary analysis, using total healthcare costs and HAM-D scores as the measure of effect, ISTDP was associated with lower cost and more improvement in HAM-D scores at 18 months using a discount rate of 1.5% (See Table 4). Alternative discount rates of 0% and 3% again did not substantially affect findings.

Overall, results of sensitivity analyses revealed similar findings. When high volume service users were removed from the dataset and replaced with the group average total cost over the 18 months of the trial, differences in total group costs remained non-significant. Furthermore, results were sensitive to methods of handling missing data. The MI approach in the reference case analysis yielded more treatment effect for ISTDP than a mean interpolation approach, though in both cases ISTDP was more effective.

Probabilistic analysis demonstrated ISTDP cost savings in 2.5% of PA iterations and improved QALY in 70.3% of PA iterations. For ISTDP, at a willingness to pay (WTP) of $25,000 per QALY, 64.5% of PA iterations were cost-effective and at a WTP of $50,000 per QALY, 67.3% of PA iterations were cost-effective. In secondary analysis, ISTDP was cost savings in 2.5% of PA iterations and more effective in 99.5% of PA iterations. For ISTDP, at a WTP of $100 for a 1-point improvement in HAM-D scores, 88.1% of PA iterations were cost-effective; at a WTP of $500 for a 1-point improvement in HAM-D scores, 98.3% of PA iterations were cost-effective.

4. Discussion

The Halifax Depression Study RCT examined the efficacy and cost-effectiveness of time-limited ISTDP for secondary care patients with TRD at short- and medium-term follow-up. We previously reported that in the short-term, ISTDP was superior to CMHT treatment. After 6 months treatment, improvements in depression scores for those receiving ISTDP were greater than for patients receiving CMHT treatment (Town et al., 2017).

At the 18-month follow-up assessment, the significant improvements in the ISTDP group post-treatment had been maintained. The within group ISTDP effects sizes were in the large range (Cohen's *d:* HAM-D = 1.80; PHQ-9 = 1.66). This study is the first RCT to demonstrate sustained effectiveness of an STPP for TRD at 18 months follow-up. Based on the trend of increased antidepressant prescribing in developed countries (Lubian et al., 2016; Olfson and Marcus, 2009) and no evidence of reduction in antidepressants following other evidence-based psychotherapies for TRD (Wiles et al., 2016), it is significant that a quarter of patients in the ISTDP group had stopped all medications at 18 months. This expands the consideration for psychotherapy approaches for this complex and refractory condition to include ISTDP. It remains that trained therapists are typically in short supply with long waiting lists. The current findings justify recommending investment in training of therapists in this brief treatment modality.

The numerical remission rates following ISTDP at 18 months (40%) are comparable to the largest remission rates at 12 months in other published RCTs for TRD (40% (Wiles et al., 2013); 37.5% (Eisendrath et al., 2016)). The remission rates at longer-term follow-up reported in previous trials for TRD are lower (28% at 46 months (Wiles et al., 2016); 14.9% at 42 months (Fonagy et al., 2015)) than those at 18 months following ISTDP. Based on the remission rates reported over time in the CoBALT study (Wiles et al., 2016), the effectiveness of CBT for TRD may decline over long-term follow-up. In residual depression, the effects of CBT in preventing relapse and recurrence were initially found to persist, but were lost at longer-term follow-up (Paykel et al., 2005). Although the Tavistock Depression Study found that decrease in depression scores continued after long-term psychoanalytic psychotherapy, 18 months post-treatment remission rates were 'infrequent' (Fonagy et al., 2015). It is unclear whether smaller treatment effects at long-term follow-up based on the complex needs of people with TRD are to be expected. Future research needs to better understand if therapy could be optimised, extended or medically augmented to facilitate remission.

As predicted, we observed a significant difference in treatment efficacy between groups on depression - but not for secondary outcome measures. In this study, significant improvement from baseline to 18 months was seen in both treatments on symptoms of generalized anxiety, somatic symptoms and

general well-being. One possible explanation for small observed differences between groups on these secondary measures is that this time-limited format of ISTDP was designed specifically to focus on depressive symptoms, and it might have only had a non-specific effect in certain domains similar to that observed in the CMHT treatment. Within group changes on these measures were modest, suggesting that treatment for TRD can be optimised to achieve gains on these other measures.

We previously noted that the between-group difference in efficacy could be related to ISTDP participants receiving a greater treatment dosage (Town et al., 2017). However, during the 12-month follow-up, participants in the CMHT group were more likely to receive psychiatric medication adjustments and talk therapy, such that the mean number of sessions per patient during the 18-month study duration was not significantly different between groups. Therefore, the number of sessions likely did not influence the efficacy findings; yet, it remains possible that treatment session frequency influenced therapeutic effectiveness (Cuijpers et al., 2013). While the effectiveness of the psychotherapy delivered in CMHTs could have been improved with weekly sessions, some evidence indicates talk psychotherapy for depression can be optimized with twice weekly sessions at the start of treatment (Bruijniks et al., 2020). The smaller between-groups effect sizes on depression measures reported here at the 6- and 18-month assessments, compared to those previously observed at post-treatment using linear modelling, may be a product of the more sophisticated non-linear exponential decay model utilised, which enables the modelling of convergence to an asymptote rather than the unrealistic assumption of continuous linear decrease in depression. To avoid over-estimating treatment effects in longitudinal studies with multiple post-treatment measurements, psychotherapy researchers should consider this analytic approach for modelling the decreasing rates of change post-treatment.

Using non-linear modelling, the current results comparing time-limited ISTDP versus an active CMHT treatment providing an equivalent mean number of psychotherapy sessions plus medication treatment augmentation, showed an average difference between groups of 4.8 points on the HAM-D-17 measure at 18 months follow-up favouring ISTDP. This difference is twice the mean antidepressant-placebo difference of 2 HAM-D points seen at the end of drug treatment (Cipriani et al., 2018). While it has been pointed out that reliance on subjective measures of outcomes in depression and statistically significant group differences have led to the over-estimation of antidepressant treatment effects (Hengartner and Plöderl, 2018), we point to the 40% remission rate at 18 months post treatment in this study, in a sample with high rates of multi-morbidity and previous failed treatments, to indicate the clinical relevance of these findings.

Healthcare costs associated with TRD are high (Fostick et al., 2010; Olchanski et al., 2013) and psychotherapy treatments are expensive. Findings suggest that ISTDP may be a cost-effective alternative to CMHT for secondary treatment of refractory depression. Findings suggest that ISTDP was associated with similar costs and superior effectiveness in both the primary and secondary analyses. PA in the primary analyses suggested that there was a 64.5% probability of ISTDP being cost-effective compared to CMHT at a WTP/QALY of $25,000.

The strengths of the Halifax study design, alongside its limitations, have been previously outlined (Town et al., 2017). In particular, including a proponent of CMHT delivered care within the study team would have reduced the likelihood of an allegiance effect (Luborsky et al., 1999) in this project. We considered this randomised controlled study a stringent test of the real-world effectiveness of a time-limited psychotherapy protocol compared to usual care delivered over 18 months by secondary care CMHTs. To our knowledge, it is the first to examine both longer-term outcomes and cost effectiveness of a STPP approach for TRD. The results of the clinical outcome data are limited by missing data at follow-up assessment. In the cost-effectiveness analyses, collection of participants' health care service use data from provincial administrative databases and health records largely negated this issue, although this also meant analyses were limited to the available data. This economic evaluation is subject to several limitations. Notably, more rigorous costing would be of benefit in future study. The present study did not collect all overhead costs associated with treatments and as a result likely understates the cost associated with the models of care evaluated. As ISTDP appeared to use more services up front but CMHT appeared to use more services in the long-run, analysis using a longer time horizon would be of benefit. The present study also collected costs related to mental health services only. As depression may impact other areas of health and social care, broader categories of cost would be of interest in future study (McCrone et al., 2017). The study's sample size was not chosen to inform the economic evaluation. Future study with larger sample size would be of value, specifically for analysing cost data which tends to be skewed.

Conflict of Interest Declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Author Statement

Role of funding source

This study was funded by the Dalhousie University Department of Psychiatry, a charitable donation provided through Nova Scotia Research Foundation, and ongoing support from Nova Scotia Healthcare Authority. These funding sources had no involvement in the design, implementation, analysis, interpretation of data, or writing of the report. Portions of the service use data used in this report were made available by Health Data Nova Scotia of Dalhousie University. Although this research analysis is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness.

Contributors

JT, AA and DB conceptualized and designed the trial. CS and PB analysed and interpreted the data alongside JT. JT drafted the manuscript, to which all authors contributed significantly. All authors approved the final manuscript.

Acknowledgements

The authors thank all of the participants, therapists, research assistants and administrative staff who participated in the study. In particular, we thank Dana Jakeman for her work as lead research assistant.

References

Abbass, A., 2015. Reaching through Resistance. Seven Leaves Press, Kansas City.
Barkham, M., Gilbert, N., Connell, J., Marshall, C., Twigg, E., 2005. Suitability and utility of the CORE-OM and CORE-A for assessing severity of presenting problems in psychological therapy services based in primary and secondary care settings The British Journal of Psychiatry 186, 239-246.
Bech, P., Engelhardt, N., Evans, K., Kalali, A., Kobak, K., Lipsitz, J., Olin, J., Pearson, J., Rothman, M., Williams, J.B.W., 2003. GRID-HAM-17 GRID-HAM-21 Structured Interview Guide International Society for CNS Drug Development, San Diego, CA, USA.
Bruijniks, S.J.E., Lemmens, L., Hollon, S.D., Peeters, F., Cuijpers, P., Arntz, A., Dingemanse, P., Willems, L., van Oppen, P., Twisk, J.W.R., van den Boogaard, M., Spijker, J., Bosmans, J., Huibers, M.J.H., 2020. The effects of once- versus twice-weekly sessions on psychotherapy outcomes in depressed patients. Br J Psychiatry, 1-9.
Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Leucht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J.P.A., Geddes, J.R., 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet (London, England) 391, 1357-1366.
Cuijpers, P., Huibers, M., Daniel Ebert, D., Koole, S.L., Andersson, G., 2013. How much psychotherapy is needed to treat depression? A metaregression analysis. Journal of Affective Disorders 149, 1-13.
Davanloo, H., 2000. Intensive Short-term Dynamic Psychotherapy. Wiley, Chichester.
Driessen, E., Hegelmaier, L.M., Abbass, A.A., Barber, J.P., Dekker, J.J., Van, H.L., Jansma, E.P., Cuijpers, P., 2015. The efficacy of short-term psychodynamic psychotherapy for depression: A meta-analysis update. Clin Psychol Rev 42, 1-15.
Eisendrath, S.J., Gillung, E., Delucchi, K.L., Segal, Z.V., Nelson, J.C., McInnes, L.A., Mathalon, D.H., Feldman, M.D., 2016. A Randomized Controlled Trial of Mindfulness-Based Cognitive Therapy for Treatment-Resistant Depression. Psychotherapy and Psychosomatics 85, 99-110.
Fava, M., 2003. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 53, 649-659.
Fonagy, P., Rost, F., Carlyle, J.A., McPherson, S., Thomas, R., Pasco Fearon, R.M., Goldberg, D., Taylor, D., 2015. Pragmatic randomized controlled trial of long-term psychoanalytic psychotherapy for treatment-resistant depression: the Tavistock Adult Depression Study (TADS). World Psychiatry 14, 312-321.
Fostick, L., Silberman, A., Beckman, M., Spivak, B., Amital, D., 2010. The economic impact of depression: Resistance or severity? European Neuropsychopharmacology 20, 671-675.
Hakkaart-van Roijen, L., 2002. Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P). iMTA institute for Medical Technology Assessment, Rotterdam.
Hamilton, M., 1967. Development of a rating scale for primary depressive illness The British Journal of Social and Clinical Psychology 6, 278-296.
Hengartner, M.P., Plöderl, M., 2018. Statistically Significant Antidepressant-Placebo Differences on Subjective Symptom-Rating Scales Do Not Prove That the Drugs Work: Effect Size and Method Bias Matter! Frontiers in psychiatry 9, 517-517.

Hilsenroth, M.J., Blagys, M.D., Ackerman, S.J., Bonge, D.R., Blais, M.A., 2005. Measuring Psychodynamic-Interpersonal and Cognitive-Behavioral Techniques: Development of the Comparative Psychotherapy Process Scale. Psychotherapy: Theory, Research, Practice, Training 42, 340.
Horowitz, L.M., Alden, L.E., Wiggins, J.S., Pincus, A.L., 2000. Inventory of Interpersonal Problems, London.
Kroenke, K., Spitzer, R.L., 2002. The PHQ-9: A new depression diagnostic and severity measure Psychiatric Annals 32, 509-521.
Kroenke, K., Spitzer, R.L., Williams, J.B., 2001.
The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosomatic Medicine 64, 258-266.
Kubitz, N., Mehra, M., Potluri, R.C., Garg, N., Cossrow, N., 2013. Characterization of treatment resistant depression episodes in a cohort of patients from a US commercial claims database. PLoS One 8, e76882.
Lam, R.W., Kennedy, S.H., Grigoriadis, S., McIntyre, R.S., Milev, R., Ramasubbu, R., Parikh, S.V., Patten, S.B., Ravindran, A.V., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. J Affect Disord 117 Suppl 1, S26-43.
Lubian, K., Weich, S., Stansfeld, S., Bebbington, P., Brugha, T., Spiers, N., McManus S, C., C., 2016. Mental health treatment and services, In: McManus, S., Bebbington, P., Jenkins, R., Brugha, T. (Eds.), Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014
. NHS Digital, Leeds.

Luborsky, L., Diguer, L., Seligman, D.A., Rosenthal, R., Krause, E.D., Johnson, S., Halperin, G., Bishop, M., Berman, J.S., Schweizer, E., 1999. The Researcher's Own Therapy Allegiances: A “Wild Card” in Comparisons of Treatment Efficacy. Clinical Psychology: Science and Practice 6, 95-106.
McCrone, P., Rost, F., Koeser, L., Koutoufa, I., Stephanou, S., Knapp, M., Goldberg, D., Taylor, D., Fonagy, P., 2017. The economic cost of treatment-resistant depression in patients referred to a specialist service. Journal of Mental Health, 1-7.
Murray, C.J.L., Lopez, A.D., 1997. The Global Burden of Disease. A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020. Harvard University Press, Cambridge, Massachussetts.
Olchanski, N., McInnis Myers, M., Halseth, M., Cyr, P.L., Bockstedt, L., Goss, T.F., Howland, R.H., 2013. The Economic Burden of Treatment-Resistant Depression. Clinical Therapeutics 35, 512-522.
Olfson, M., Marcus, S.C., 2009. National patterns in antidepressant medication treatment. Archives of General Psychiatry 66, 848-856.
Paykel, E.S., Scott, J., Cornwall, P.L., Abbott, R., Crane, C., Pope, M., Johnson, A.L., 2005. Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. Psychological Medicine 35, 59-68.
Pinheiro, J.C., Bates, D.M., 2001. Mixed-effects models in S and S-plus. Springer-Verlag, New York.
Rubin, D.B., 1987. Multiple imputation for nonresponse in surveys. John Wiley and Sons, New York.
Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 163, 1905-1917.
Singer, J.C., Willett, J.B., 2003. Applied longitudinal data analysis: Modelling change and event occurrence. Oxford University Press, New York.

Souza, L.H., Salum, G.A., Mosqueiro, B.P., Caldieraro, M.A., Guerra, T.A., Fleck, M.P., 2016. Interpersonal psychotherapy as add-on for treatment-resistant depression: A pragmatic randomized controlled trial. J Affect Disord 193, 373-380.
Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder The GAD-7 Archives of Internal Medicine 166, 1092-1097.
Town, J.M., Abbass, A., Stride, C., Bernier, D., 2017. A randomised controlled trial of Intensive Short-Term Dynamic Psychotherapy for treatment resistant depression: the Halifax Depression Study. Journal of Affective Disorders 214, 15-25.
Trivedi, R.B., Nieuwsma, J.A., Williams, J.W., Jr., 2011. Examination of the utility of psychotherapy for patients with treatment resistant depression: a systematic review. J Gen Intern Med 26, 643-650.
Ware, J., Jr., Kosinski, M., Keller, S.D., 1996. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 34, 220-233.
WHO, 2013. Mental health action plan 2013-2020. WHO, Geneva, Switzerland.
Wiles, N., Thomas, L., Abel, A., Ridgway, N., Turner, N., Campbell, J., Garland, A., Hollinghurst, S., Jerrom, B., Kessler, D., Kuyken, W., Morrison, J., Turner, K., Williams, C., Peters, T., Lewis, G., 2013. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. Lancet 381, 375-384.
Wiles, N.J., Thomas, L., Turner, N., Garfield, K., Kounali, D., Campbell, J., Kessler, D., Kuyken, W., Lewis, G., Morrison, J., Williams, C., Peters, T.J., Hollinghurst, S., 2016. Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBalT randomised controlled trial. The Lancet Psychiatry 3, 137-144.

Figure 1: CONSORT Diagram of patient flow through Halifax Depression Study

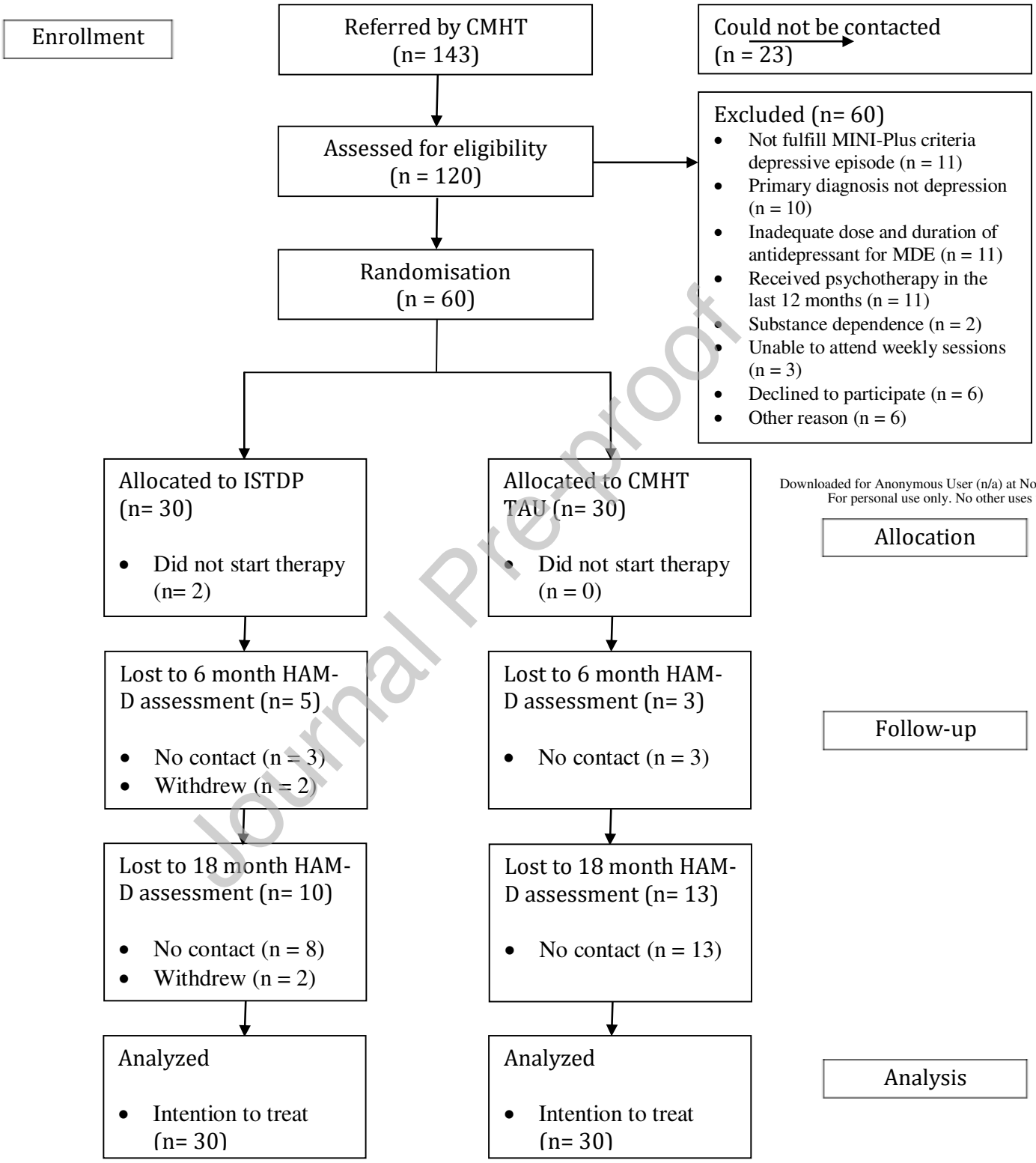


Table 1: Treatment Received 7-18 months Summary

	ISTDP (N=30) N	CMHT (N=28) N	Statistic	*p*-value
Talking Therapy				
Any Talk Therapy (%)	10 (33.3)	21 (75.0)	$\chi^2 = 10.106$	.001**
Mean Sessions (SD)	2.9 (6.1)	8.5 (7.7)	$t = 3.061$	.003**
1:1 Therapy (%)	9 (30.0)	20 (71.4)	$\chi^2 = 9.943$	.002**
1:1 Mean Sessions (SD)	2.3 (5.3)	6.1 (6.8)	$t = 2.401$	.020*
ISTDP (%)	1 (3.3)	0	$\chi^2 = 0.950$	.330
CBT (%)	1 (3.3)	9 (32.1)	$\chi^2 = 8.424$	.004**
Counselling (%)	7 (23.3)	9 (32.1)	$\chi^2 = 0.563$	.453
Psychodynamic (%)	2 (6.7)	2 (7.1)	$\chi^2 = 0.005$	.943
Group CBT (%)	2 (6.7)	9 (32.1)	$\chi^2 = 6.116$	.013*
CBT Group Mean Sessions (SD)	0.6 (2.3)	2.9 (4.9)	$t = 2.269$	.029*
Other Interventions				
Psychosocial Intervention (%)	1 (3.3)	6 (21.4)	$\chi^2 = 4.469$	.035*
Guided Self-help (%)	1 (3.3)	5 (17.9)	$\chi^2 = 4.603$	.032*
Peer support group (%)	0	3 (10.7)	$\chi^2 = 3.390$	.066
Meditation group (%)	0	2 (7.1)	$\chi^2 = 2.219$	.136
Healthy living plans (%)	1 (3.3)	2 (7.1)	$\chi^2 = 0.429$	.513
A&E urgent care (%)	1 (3.3)	2 (7.1)	$\chi^2 = 0.429$	.513
Mental Health Day Hospital (%)	1 (3.3)	1 (3.6)	$\chi^2 = 0.002$	.960
Inpatient Admission (%)	1 (3.3)	1 (3.6)	$\chi^2 = 0.002$	.960
Psychiatry (%)	3 (10.0)	6 (21.4)	$\chi^2 = 1.443$	.230
Psychiatric Medications				
Antidepressants (%)	22 (73.3)	27 (96.4)	$\chi^2 = 5.893$	.015*
Anxiolytics (%)	9 (30.0)	13 (46.4)	$\chi^2 = 1.660$	.198
Antipsychotics (%)	1 (3.3)	7 (25.0)	$\chi^2 = 5.718$	.017*
Hypnotics (%)	4 (13.3)	6 (21.4)	$\chi^2 = 0.665$	.415
Medications added/changed (%)	7 (23.3)	15 (53.6)	$\chi^2 = 5.625$	.018*
Medications stopped/reduced (%)	9 (30.0)	4 (14.3)	$\chi^2 = 2.057$	.152
T6 N of medications (mean/SD)	1.3 (1.2)	2.4 (1.2)	$t = 3.683$	.001**
T6 Zero medications (%)	8 (26.7)	0	$\chi^2 = 8.661$	.003**

Note: Statistical comparisons of differences between groups were conducted on proportions using the chi-square test and of means with Student t-tests. CBT- cognitive behaviour therapy; ISTDP- intensive short-term dynamic psychotherapy; CMHT- community mental health team
*p < 0.05, **p < 0.01

Table 2: Estimated fixed effects coefficients (B) and 95% Confidence Intervals (CI) from exponential decay growth models with random initial value and change parameters, and study group as a predictor of variation in initial value and change

	Outcome: HAM-D		Outcome: PHQ-9	
Model Parameter	B	95% CI	B	95% CI
init.(Intercept)	24.212*	(22.031, 26.394)	20.409*	(18.462, 22.356)
init.GROUP	-0.636	(-3.716, 2.443)	-1.168	(-3.919, 1.583)
diff.(Intercept)	6.370*	(3.484, 9.255)	5.938*	(3.057, 8.818)
diff.GROUP	4.184*	(0.148, 8.220)	4.082*	(0.151, 8.012)
rate	1.233*	(0.662, 1.804)	1.091*	(0.570, 1.613)

N = 279 observations from 60 individuals across 6 time points.
*p < 0.05,

Table 3: Effect sizes (Cohen's *d*) for group differences in HAM-D and PHQ-9 outcomes at each time point

Outcome measure	Time point	ISTDP		CMHT		Pooled SD	Mean Difference	Cohen's *d*	95% CI for Cohen's *d*	
		mean†	SD	mean†	SD					
HAM-D	1: Baseline	23.576	5.309	24.212	5.169	5.240	-0.636	-0.121	(-0.625,	0.388)
	2: 3 months	16.099	8.088	19.700	7.833	7.966	-3.601	-0.452	(-0.980,	0.101)
	3: 6 months	13.919	8.995	18.384	6.648	7.863	-4.465	-0.568	(-1.106,	0.002)
	4: 9 months	13.284	7.358	18.000	8.514	7.879	-4.717	-0.599	(-1.228,	0.064)
	5: 12 months	13.098	7.959	17.889	8.782	8.322	-4.790	-0.576	(-1.222,	0.103)
	6: 18 months	13.044	6.529	17.856	8.569	7.531	-4.812	-0.639	(-1.283,	0.041)
PHQ-9	1: Baseline	19.241	4.639	20.814	4.843	4.742	-1.572	-0.332	(-0.832,	0.187)
	2: 3 months	12.586	6.222	16.242	7.071	6.652	-3.656	-0.550	(-1.082,	-0.014)
	3: 6 months	10.352	7.465	14.966	6.353	6.955	-4.614	-0.663	(-1.226,	-0.064)
	4: 9 months	9.602	6.440	14.610	8.132	7.127	-5.008	-0.703	(-1.346,	-0.020)
	5: 12 months	9.350	6.712	14.510	7.816	7.206	-5.161	-0.716	(-1.365,	-0.027)
	6: 18 months	9.265	7.291	14.483	7.644	7.449	-5.217	-0.700	(-1.357,	-0.005)

†Effect size computed using estimated marginal means, and the SD of the outcome variable from the observed data at the respective timepoint. N = 279 observations from 60 individuals across 6 time points

Figure 2: HAM-D and PHQ outcomes - estimated marginal means from exponential decay model with study group predicting initial value and difference parameters (table 3, model 4b), and sample means

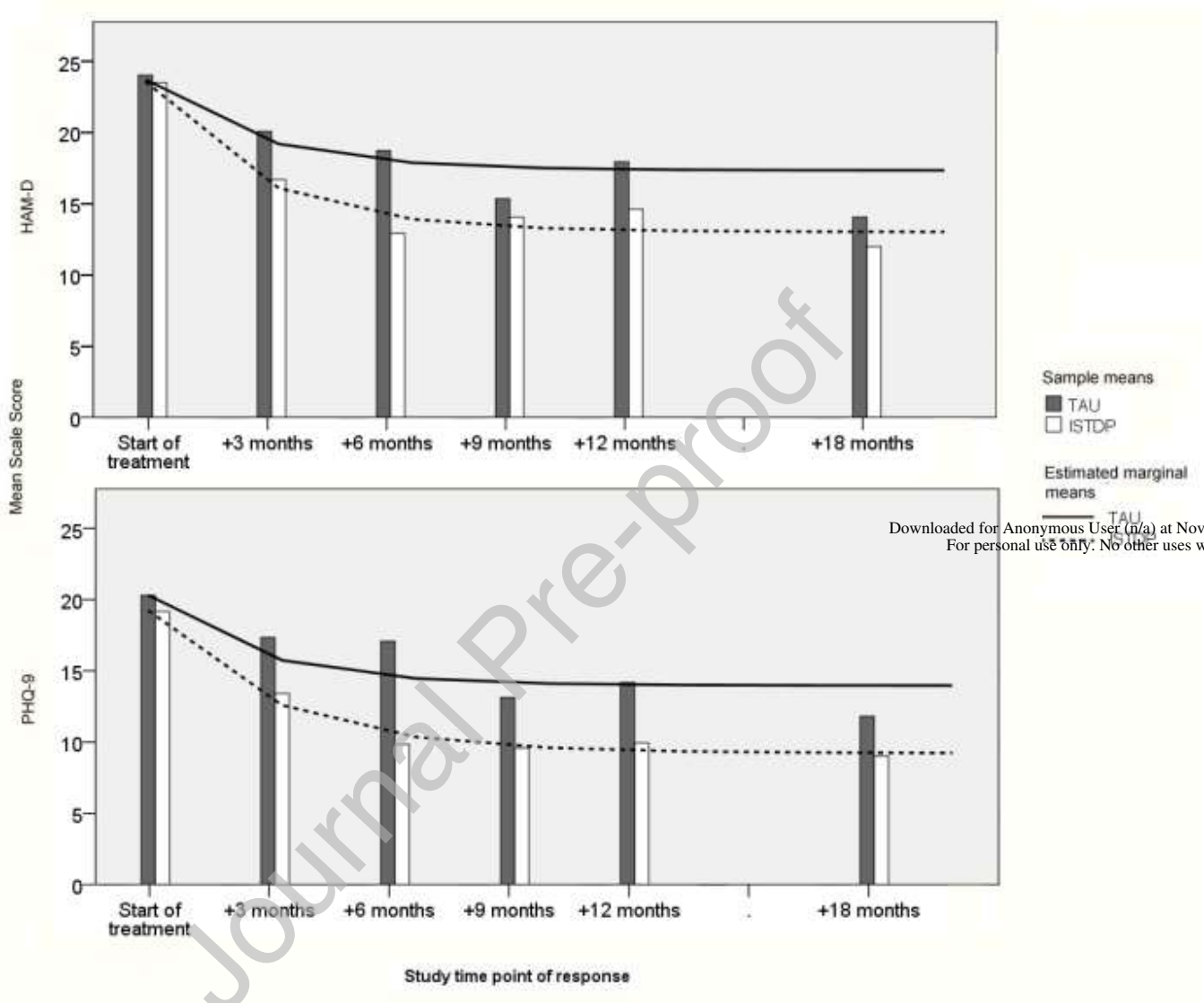


Table 4. Incremental Cost-effectiveness Ratios

Treatment	Average Cost	Δ Cost	Average Effectiveness	Δ Effectiveness	ICER
Reference Case Analysis (QALY at 18 months)					
CMHT	$5,177.60	-$503.43[A]	0.87	0.03[A]	Dominant (ISTDP)
ISTDP	$4,674.17		0.90		
Secondary Analysis (HAM-D at 18 months)					
CMHT	$5,177.60	-$503.43[A]	8.569	-2.04[A]	Dominant (ISTDP)
ISTDP	$4,674.17		6.529		

[A] This difference was in favor of ISTDP.