Mentalization-Based Treatment Versus Specialist Treatment as Usual for Borderline Personality Disorder: Economic Evaluation Alongside a Randomized Controlled Trial With 36-Month Follow-Up

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MENTALIZATION-BASED TREATMENT VERSUS SPECIALIST TREATMENT AS USUAL FOR BORDERLINE PERSONALITY DISORDER: ECONOMIC EVALUATION ALONGSIDE A RANDOMIZED CONTROLLED TRIAL WITH 36-MONTH FOLLOW-UP

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The authors present an economic evaluation performed alongside a randomized controlled trial of mentalization-based treatment in a day hospital setting (MBT-DH) versus specialist treatment as usual (S-TAU) for borderline personality disorder (BPD) with a 36-month follow-up period. Ninety-five patients from two Dutch treatment institutes were randomly assigned. Societal costs were compared with the proportion of BPD remissions and quality-adjusted life years (QALYs) measured using the five-dimensional EuroQol instrument. The incremental societal costs for one additional QALY could not be calculated. The costs for one additional BPD remission with MBT-DH are approximately €29,000. There was a 58% likelihood that MBT-DH leads to more remitted patients at additional costs

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Patrick Luyten has been involved in the training and dissemination of mentalization-based treatments. The other authors declare that they have no competing interests.

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compared with S-TAU, and a 35% likelihood that MBT-DH leads to more remissions at lower costs. MBT-DH is not cost-effective compared with S-TAU with QALYs as the outcome, and slightly more cost-effective than S-TAU at 36 months with BPD symptoms as the outcome.

Keywords: economic evaluation, mentalization-based treatment, borderline personality disorder, randomized controlled trial

Borderline personality disorder (BPD) is one of the most prevalent mental disorders in psychiatric populations (Leichsenring, Leibing, Kruse, New, & Leweke, 2011; Paris, 2010) and is associated with low quality of life (Soeteman, Verheul, & Busschbach, 2008), high psychiatric comorbidity (Barrachina et al., 2011; Skodol et al., 1999; Trull, Sher, Minks-Brown, Durbin, & Burr, 2000; Zanarini, 1998), and, in addition, high socioeconomic burden (Laurenssen et al., 2016; Soeteman, Hakkaart-van Roijen, Verheul, & Busschbach, 2008). In pure monetary terms, the projected annual average societal cost for a BPD patient based on 2014 prices is approximately €15,000 per year, based on work by Soeteman, Hakkaart-van Roijen, et al. (2008; €13,088 in the year 2005) and Laurenssen et al. (2016; €16,879 per year).

International treatment guidelines (Dutch Committee of Guideline-Development for Mental Health Care, 2008; National Institute for Health and Clinical Excellence, 2009) and a Cochrane review (Stoffers et al., 2012) suggest that mentalization-based treatment (MBT; Bateman & Fonagy, 2004) in a day hospital setting (MBT-DH) or in an outpatient setting is a preferred treatment for BPD, given the strong evidence base, which for BPD is exceeded only by that for dialectical behavior therapy (DBT; Stoffers et al., 2012). MBT is a psychodynamic treatment based on attachment and mentalizing approaches. *Mentalizing* refers to the capacity to interpret the self and others in terms of internal mental states such as feelings, emotions, wishes, desires, attitudes, and values (Laurenssen et al., 2014). The first randomized controlled trial (RCT) of MBT was conducted by Bateman and Fonagy (see Bateman & Fonagy, 1999, 2001, 2008). This first RCT was criticized for its lack of a competitive therapy as a control and the role of the developers of MBT themselves as the primary investigators. Subsequently, the developers performed RCTs with a competitive control condition, again showing favorable results for outpatient MBT (Bateman & Fonagy, 2009; Robinson et al., 2016; Rossouw & Fonagy, 2012). RCTs independent of the developers of MBT have shown more modest results (Jørgensen et al., 2013, 2014). A matched-control design study (Bales et al., 2015) confirmed the effectiveness of MBT up to 36-month follow-up.

There are still few studies on the cost-effectiveness of MBT. Favorable economic outcomes were presented by Bateman and Fonagy (2003) based on their RCT, showing that during treatment the costs of MBT were similar to those of the control condition, whereas costs in the MBT condition were substantially lower after treatment completion. A problem with the interpretation of these results was that the control intervention was not specifically aimed at BPD; furthermore, the economic evaluation performed by Bateman and Fonagy (2003) was not performed according to state-of-the art guidelines for cost-effectiveness studies. Attempts to replicate these results using more conventional methods led to results surrounded by uncertainty (Brazier et al., 2006). Therefore, a state-of-the-art health economic evaluation of MBT using a relevant control condition and a long-term follow-up is needed.

In 2018, Laurenssen et al. conducted an RCT independently of the developers of MBT and concluded that MBT-DH was equally as effective as specialist treatment as usual (S-TAU) at 18-month follow-up. Recently, the 36-month follow-up data from this RCT became available. These data allow us to test whether initial higher costs of MBT are offset by lower costs and better clinical outcomes at long-term follow-up. A cost-effectiveness study by Soeteman et al. (2010) with a 5-year time horizon revealed the contrary, that is, that the higher treatment costs of day hospital treatments for BPD, including MBT, are not offset by a reduction in costs of health care utilization and productivity losses when compared with outpatient treatment, at a willingness-to-pay threshold of €40,000 per quality-adjusted life year (QALY). According to the Netherlands Health Care Institute, a willingness-to-pay threshold of €50,000 is more suitable for patients with a disease burden comparable to the studied population (Zorginstituut Nederland, 2015). Over a 5-year time horizon, day hospitalization was more effective in terms of QALYs and more cost-effective, at a price of €56,325 per QALY, compared with outpatient care—just above the €50,000 threshold. Thus, it might be possible that, especially in the long term, MBT-DH is more cost-effective than S-TAU.

In the current article, we present an economic evaluation performed alongside the RCT by Laurenssen et al. (2018), which compared the costs and effects of MBT-DH and S-TAU over a 36-month follow-up period. The evaluation consists of a cost-utility analysis from a societal perspective, in which the utilities have been expressed in QALYs. To align with the more traditional outcomes in psychology and psychiatry, we have also performed a cost-effectiveness analysis in which the effects have been expressed as the proportion of patients having a low/subthreshold (≤ 15) Borderline Personality Disorder Severity Index version IV (BPDSI) score (Arntz et al., 2003).

METHOD

For the design and reporting of this economic evaluation, we adhered to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Husereau et al., 2013) and to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guideline for economic evaluation alongside RCTs (Ramsey et al., 2015).

PARTICIPANTS, ALLOCATION, AND ASSESSMENTS

Participants were 95 patients meeting the criteria for a BPD diagnosis as assessed by the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II) (Weertman, Arntz, & Kerkhofs, 2000), and a total score on the BPDSI (Arntz et al., 2003) of at least 20, reflecting severe BPD. All patients had been referred to one of two mental health care institutes in Amsterdam (Arkin or De Viersprong). Exclusion criteria were schizophrenia, bipolar disorder, substance use disorders requiring specialist treatment, organic brain disorder, IQ <80, and inadequate mastery of the Dutch language. Patients who met the inclusion criteria and provided written informed consent were randomly assigned to receive MBT-DH or S-TAU. Patients completed the baseline BPDSI before randomization and before diagnosis; all other baseline assessments were completed after randomization and after diagnosis. Treatment started at around the time the baseline assessments were completed. Follow-up interviews and assessments were conducted every 6 months until 36-month follow-up. The protocol of this study has been published elsewhere (Laurenssen et al., 2014). This study was approved by a Medical Ethics Review Committee in the Netherlands and is registered in the trial register as # NL26308.097.09, and complied with the Helsinki Declaration 1975, as revised in 2008.

INTERVENTIONS

MBT-DH comprises an intensive day hospitalization program of a maximum of 18 months followed by up to 18 months of maintenance mentalizing (group) therapy. The day hospital program, which takes place for 6 hours per day, 5 days per week, includes (a) implicit mentalizing groups (daily group psychotherapy and weekly individual psychotherapy, and individual crisis planning from a mentalizing perspective) and (b) explicit mentalizing groups (art therapy twice a week, mentalizing cognitive group therapy, and writing therapy). Each week ends with a social hour and a community meeting. Patients can also consult a psychiatrist once a week and medication is offered according to American Psychiatric Association guidelines. The treatment aims of MBT-DH are to (a) engage patients in treatment; (b) reduce psychiatric symptoms, particularly self-harm and parasuicidal behavior; (c) improve social and interpersonal functioning; and (d) foster more appropriate health care usage and prevent hospital admissions and (prolonged) inpatient care. To achieve these aims, components of MBT-DH focus on enhancing the patients' mentalizing capacity (Laurenssen et al., 2014).

S-TAU comprises mainly outpatient manualized treatments for patients with severe personality disorders, with varying treatment length and duration. S-TAU is an eclectic intervention, consisting of supporting and structuring sessions, extensive diagnostic investigations, writing a crisis plan, family interventions, Systems Training for Emotional Predictability and Problem Solving (Blum et al., 2008) or Linehan training, social skills training, aggression/impulse regulation training, cognitive schema-focused or traditional insight-oriented treatment, pharmacotherapy, and/or inpatient treatment. If possible, patients in the S-TAU condition are treated by the Municipality Mental Health Crisis Service; otherwise, patients are referred to other treatments that meet their specific needs and wishes (see Laurenssen et al., 2014, for more details). However, S-TAU patients did not receive MBT, and the S-TAU intervention is less intensive than the MBT-DH intervention in terms of engagement and time spent in therapy.

RESOURCE USE AND VALUATION

Health care utilization, use of medication, and productivity losses were measured using the first section of the Trimbos Questionnaire for Costs associated with Psychiatric illness (TiC-P; Hakkaart-van Roijen, van Straten, Donker, & Tiemens, 2002). This instrument is validated for economic evaluations in populations of psychiatric patients (Bouwmans et al., 2013). Using this section of the TiC-P, we collected the number of contacts with health professionals and the frequency of informal care for the 6-month period before the follow-up interviews. The TiC-P has a 4-week recall period, which was linearly extrapolated to the 6-month period between the consecutive follow-up interviews, in line with the approach used by Hakkaart-van Roijen et al. (2007). Using the TiC-P, all health care contacts except MBT-DH- or S-TAU-related health care contacts were collected; the MBT-DH and S-TAU contacts were collected from the electronic patient records of the two participating treatment centers.

Standard unit cost prices for the Netherlands (Zorginstituut Nederland, 2016) were used to value health care resource utilization by multiplying the number of contacts with the reference costs per contact. Medication costs were valued based on the reported medication use. Frequency of medication use was assumed to be daily unless otherwise noted. Unit costs per dose of medication were extracted from the Netherlands Ministry of Health registry for cost prices of medication (Farmatec, 2016).

The second section of the TiC-P is the Short Form-Health and Labor Questionnaire (SF-HLQ). This questionnaire assesses whether the participant has worked in the previous 2 weeks and whether he or she has been absent from work (absenteeism) or has functioned suboptimally at work due to illness (presenteeism). Productivity losses in hours were multiplied by an estimate of averaged labor costs of €37.90 for men and €31.60 for women (Zorginstituut Nederland, 2016). Productivity losses were valued using the friction cost method, with a maximum friction costs period of 85 days (based on Zorginstituut Nederland, 2016) and an elasticity factor of 0.8 (Koopmanschap, Rutten, van Ineveld, & van Roijen, 1995). Another source of public costs assessed in this economic evaluation was the use of justice system resources. We collected all self-reported police and justice-related contacts of patients, and we valued these contacts according to the justice system costs valuation by Drost, Paulus, Ruwaard, and Evers (2014).

All future costs as seen from the date of randomization were discounted at an annual rate of 4% (Zorginstituut Nederland, 2016). Dutch unit prices were converted to Organisation for Economic Co-operation and Development (OECD) standard purchasing power parities for the study's index year, 2014 (123% for the Netherlands) (OECD, 2019).

EFFECT MEASURES

The effect measure for the cost-utility analysis was the number of QALYs gained between the time of randomization and 36-month follow-up. The three-level, five-dimensional EuroQol (EQ-5D-3L) quality of life instrument was used (EuroQol Group, 1990). The EQ-5D-3L comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with three levels: no problems, some problems, and extreme problems. Using the Dutch EQ-5D tariff (EQ-5D NL; Lamers, McDonnell, Stalmeier, Krabbe, & Busschbach, 2006), we converted the raw EQ-5D-3L scores to health utilities. Using the area under the curve method with linear interpolation, we integrated the repeated measures of these health utilities over the 36-month follow-up period into the number of QALYs gained or lost for each participant. Future QALYs have been discounted at a rate of 1.5% per year (Zorginstituut Nederland, 2016). The effect measure for the cost-effectiveness analysis was the proportion of patients having a BPDSI score ≤15 at the 36-month follow-up. The BPDSI scale has a range of 0–90, with higher scores representing greater severity (Giesen-Bloo, Wachters, Schouten, & Arntz, 2010). The ≤15 criterion has been proposed as the clinical cutoff score (Giesen-Bloo et al., 2010); hence, patients with a score of 15 or lower are considered to have remitted.

DATA PREPARATIONS

All analyses were performed on an intention-to-treat basis. Missing observations in costs and effects data were handled using multiple imputation (with 50 imputations for each missing observation). Imputations were performed using the package Amelia II v. 1.7.5 (Honaker, King, & Blackwell, 2018). In the base case analysis, missing data were assumed to be missing at random (MAR). The MAR pattern is conventionally assumed when applying common missing data approaches such as multiple imputation. Cost parameters were square root transformed before imputation and back-transformed to the original scale afterward in order to take the skewed distribution of these variables into account. First, analyses were performed on the imputed datasets separately. The outcomes of the 50 imputations were then combined using Rubin's (1987) rules. All presented results are based on the multiple imputed data, unless otherwise indicated. We used the R statistical programming environment for all analyses.

COST-EFFECTIVENESS CALCULATIONS

For all participants, we multiplied units of health care (e.g., sessions, contacts, and medication), productivity losses due to absenteeism or presenteeism, and contacts with the justice system (e.g., days of incarceration) by their associated costs. Differences in costs and effects between MBT-DH and S-TAU were calculated as the difference in cumulative costs and effects over the 36-month period of this study. In order to present the development over time of the costs and effects for the two interventions in terms of BPDSI score, remissions, quality of life, and societal costs from baseline to 36-month follow-up, generalized linear mixed models were fitted.

Next, we extracted a total of 2,500 nonparametric bootstrapped samples from the imputed data, with a number of patients per trial arm equal to the number of patients in the original dataset. For each of these bootstrapped samples, we calculated the incremental costs, incremental effects, and incremental cost-effectiveness ratio (ICER). The ICER was calculated as follows: ICER = ($Costs_{MBT\text{-}DH}$ – $Costs_{S\text{-}TAU}$) / ($Effects_{MBT\text{-}DH}$ – $Effects_{S\text{-}TAU}$), where effects were either QALYs or remission rates based on BPDSI scores. These data were also plotted on cost-effectiveness planes, which present the differences in costs and effects between MBT-DH and S-TAU in two dimensions by plotting costs against effects. The reference intervention (S-TAU) is positioned in the origin of the cost-effectiveness plane. Based on the distribution of the ICERs over the cost-effectiveness plane, cost-effectiveness acceptability curves (CEACs; van Hout, Al, Gordon, & Rutten, 1994) were drawn. CEACs show the probability that MBT-DH is more cost-effective than S-TAU as a function of the willingness to pay for one additional unit of effect (one additional QALY or one additional person whose BPD remitted). Willingness to pay can be €50,000 per QALY in the Netherlands for an intermediate burden of disease, such as BPD (Zwaap, Knies, van der Meijden, Staal, & van der Heiden, 2015).

BASE CASE, ALTERNATIVE SCENARIOS, AND SENSITIVITY ANALYSES

The base case scenario of this economic evaluation was performed from the societal perspective, using the data imputed under the MAR assumption. The societal perspective implies that all available costs were included, that is, BPD treatment costs, medication costs, all other health care costs, losses or gains in productivity of each patient, and patients' justice resource costs. In addition to this base case scenario analysis, we performed three alternative analyses. In the first, the societal perspective was taken but this time missing data were imputed under the Missing Completely At Random (MCAR) assumption, which postulates that missing observations are randomly drawn from the available data (Rubin, 1987). MCAR imputations were performed using the "random sample draw" option in the imputation package mice v. 2.30 (van Buuren & Groothuis-Oudshoorn, 2011) for R. Differences between MCAR and MAR may indicate that dropout affected the representativeness of the final sample. The second alternative analysis evaluated the cost-effectiveness of MBT-DH versus S-TAU from the health care sector perspective. In this analysis, BPD treatment costs, medication costs, and all other health care costs were included. The last alternative analysis took the narrowest costs perspective and accounted for BPD treatment costs only. In order to assess the sensitivity of our findings to misspecification of costs, one-way sensitivity analyses were performed to evaluate the impact on the ICERs of a –20% to +20% misspecification in the above-mentioned cost categories.

RESULTS

DESCRIPTIVE STATISTICS

Table 1 presents the participants' baseline characteristics. Differences between MBT-DH and S-TAU were tested using *t* tests and Pearson's chi-square test with Monte Carlo simulated *p* values where we had to deal with a low number of participants. None of the characteristics listed in Table 1 differed significantly between the two study conditions at baseline. Appendix Table A1 presents a comparison of the data completeness of the two study conditions over time.

COSTS

Table 2 presents the cumulative societal mean costs during the trial from baseline to 36-month follow-up. The psychiatric hospitalization costs associated with BPD treatment were significantly lower in MBT-DH, whereas

TABLE 1. Baseline Demographic and Clinical Characteristics of the Study Participants

	MBT-DH (*n* = 54)	S-TAU (*n* = 41)	χ^2 | t(*df*)	*p*
Age; mean (SD)	34.3 (9.5)	34.0 (10.6)	t(80.9) = 0.13	.89
Gender; *n* (%)			$\chi^2(1) = 0.10$	.8
Female	42 (77.8)	33 (80.5)		
Education; *n* (%)[a]			$\chi^2(8) = 6.77$	.49
Low/other	5 (9.4)	5 (12.2)		
Medium	23 (43.4)	20 (48.8)		
High	25 (47.2)	16 (39.0)		
Trial site; *n* (%)			$\chi^2(1) = 0.01$	1.00
Arkin	36 (66.7)	27 (65.9)		
Viersprong	18 (33.3)	14 (34.1)		
Marital status; *n* (%)			$\chi^2(6) = 6.53$	.28
Married	3 (5.6)	1 (2.4)		
Divorced	4 (7.4)	5 (12.2)		
Partner relationship	5 (9.3)	2 (4.9)		
Living together	4 (7.4)	5 (12.2)		
Single	38 (70.4)	25 (61.0)		
Other	0 (0)	3 (7.3)		
Vocational status; *n* (%)[b]			$\chi^2(8) = 3.77$	.74
Employed	13 (26.0)	5 (12.5)		
Unemployed	27 (54.0)	27 (67.5)		
Student	2 (4.0)	1 (2.5)		
Other	8 (16.0)	7 (17.5)		
BPDSI total score; mean (*SD*)	34.4 (8.3)	32.8 (7.1)	t(91.7) = 1.03	.31
EQ-5D NL score; mean (*SD*)	0.42 (0.33)	0.39 (0.27)	t(65.5) = 0.42	.67
All health care costs; mean (*SD*)	6 203 (9 531)	4 926 (9 008)	t(88.0) = 0.66	.51
Productivity costs; mean (*SD*)	500 (1 930)	572 (2 156)	t(80.9) = 0.17	.87

Note. MBT-DH = day hospital mentalization-based treatment; S-TAU = specialist treatment as usual; BPDSI = Borderline Personality Disorder Severity Index version IV; EQ-5D NL = three-level, five-dimensional EuroQol with the Dutch health utilities algorithm applied (Lamers et al., 2006).
[a]*n* = 53 (MBT-DH), the original nine levels have been reduced to three levels; for χ^2 test, the nine-level data have been used. [b]*n* = 50 (MBT-DH); *n* = 40 (S-TAU), the original nine levels have been reduced to four levels; for χ^2 test, the nine-level data have been used.

TABLE 2. Mean Costs and Bootstrapped Incremental Mean Costs per Cost Category

	MBT-DH (n = 54)		S-TAU (n = 41)		Incremental costs (95% CI)		
Cumulative cost	Mean (€)	*SD*	Mean (€)	*SD*	Median	Lower CI	Upper CI
BPD hospitalization	3,988	10,721	19,620	56,858	–15,623	–18,202	–13,228
BPD day hospital	21,130	10,396	2,589	5,169	18,543	18,099	18,979
BPD outpatient care	12,949	13,122	12,145	13,402	802	54	1,555
BPD treatment (total)	38,067	21,750	34,354	57,016	3,712	1,089	6,273
Medication	2,576	1,858	2,711	1,935	–135	–242	–25
Other health care	20,571	20,391	22,240	17,730	–1,668	–2,752	–572
Productivity	1,596	4,141	1,217	2,949	379	180	582
Justice resources	1,310	2,335	619	1,135	692	593	791
Overall societal costs	64,121	29,463	61,141	66,171	2,973	–71	6,011

Note. MBT-DH = day hospital mentalization-based treatment; S-TAU = specialist treatment as usual. Other health care refers to all other health care costs (psychiatric and/or somatic) not directly related to MBT-DH or S-TAU BPD treatment; presented costs are the full costs accrued between baseline and 36-month follow-up. CI is the confidence interval around the median. Some numbers may not add up due to rounding and bootstrapping. Due to the skewed distributions of costs, the standard deviation likely overestimates the variation in costs.

the day hospital costs associated with BPD treatment and overall treatment costs associated with BPD were significantly higher in MBT-DH compared to S-TAU. In addition, medication costs were significantly lower in MBT-DH, whereas other health care costs, productivity costs, and justice resources costs were significantly lower in S-TAU. The overall societal costs were slightly higher in MBT-DH. Figure A1 in the appendix gives more information about the societal costs for the MBT-DH and S-TAU group for each assessment point.

EFFECTS

Table 3 presents the effects of the MBT-DH and the S-TAU interventions in terms of quality of life and BPDSI score from baseline to 36-month follow-up. The Time × Group interactions for EQ-5D NL score (p = .56) and for QALYs (p = .31) were not statistically significant. The BPDSI scale scores in both conditions declined over time. Generalized linear mixed model analysis, with gender, age, and treatment center as covariates, a random intercept for patients, and a random slope for time within patients, indicated a significant Time × Group interaction, B = –1.388, SE = 0.475, t(234.4) = 2.919, p = .004. This interaction effect indicated that the decline in BPDSI score was stronger for the MBT-DH group than the S-TAU group. No Time × Group interaction effect was found for the proportion of patients whose BPD remitted (p = .10); for this model, a binomial link function was applied. For the societal costs, a significant Time × Group interaction was found, B = –1001, SE = 356.1, t(16,363) = 2.81, p = .005, indicating that the development of societal cost over time was different for the MBT-DH and S-TAU conditions—as can also be seen in Figure A1.

TABLE 3. Intervention Effects and Societal Costs per Outcome Assessment Wave

		MBT-DH		S-TAU	
Measure	Time (months)	Mean | %	*SD*	Mean | %	*SD*
BPDSI score	Baseline	34.4	8.29	32.8	7.08
	6	29.8	11.45	25.4	10.29
	12	25.4	11.65	24.8	10.07
	18	21.5	11.03	22.4	9.64
	24	19.2	10.17	21.9	10.07
	30	18.2	9.45	22.9	10.32
	36	19.5	11.12	23.7	10.09
BPDSI ≤15 (Remission)	Baseline	0.0%		0.0%	
	6	9.4%		13.6%	
	12	15.8%		18.1%	
	18	29.4%		24.7%	
	24	38.0%		25.5%	
	30	40.0%		25.6%	
	36	33.4%		19.6%	
EQ-5D NL score	Baseline	0.408	0.340	0.404	0.284
	6	0.398	0.328	0.490	0.320
	12	0.413	0.352	0.476	0.316
	18	0.452	0.354	0.509	0.313
	24	0.443	0.345	0.510	0.343
	30	0.432	0.340	0.515	0.323
	36	0.472	0.375	0.555	0.316
QALYs (cumulative)	Baseline	0	0	0	0
	6	0.200	0.138	0.221	0.116
	12	0.402	0.270	0.455	0.222
	18	0.618	0.394	0.691	0.311
	24	0.842	0.506	0.941	0.399
	30	1.060	0.605	1.119	0.489
	36	1.287	0.715	1.471	0.571
Societal costs	Baseline	€6,697	€9,728	€5,708	€9,303
	6	€14,714	€6,254	€9,737	€11,267
	12	€13,367	€9,222	€10,332	€12,202
	18	€9,580	€7,484	€10,033	€14,714
	24	€7,234	€5,820	€8,665	€10,502
	30	€6,655	€5,339	€8,426	€10,918
	36	€5,872	€5,296	€8,240	€11,955

Note. BPDSI score = Borderline Personality Disorder Severity Index version IV sum score; EQ-5D NL score = three-level, five-dimensional EuroQol with the Dutch health utilities algorithm applied (Lamers et al., 2006); QALYs is the averaged cumulative number of QALYs since baseline per patient at the end of each time point, with QALYs based on the EQ-5D NL score; Societal costs refers to the total societal costs in the 6 months prior to the data collection wave indicated by Time; all results are based on multiple imputed data.

COST-UTILITY AND COST-EFFECTIVENESS

Table 4 presents the results of the cost-utility and cost-effectiveness analysis. Figure 1 shows the cost-effectiveness planes and the CEACs associated with the base case scenario.

With regard to the cost-utility analysis, from Table 4 it can be observed that the ICER for one additional QALY could not be calculated, because for this effect measure MBT-DH is dominated by S-TAU: Patients receiving MBT-DH cost more and gained fewer QALYs than S-TAU patients. This finding is further illustrated by the cost-effectiveness plane for QALYs. It can be observed from Figure 1 that there is a 57% likelihood that MBT-DH is dominated by S-TAU (northwest quadrant), and a 35% likelihood that MBT-DH could be cost-saving (i.e., leading to fewer QALYs at lower societal costs; southwest quadrant). The likelihood that MBT-DH dominates S-TAU with regard to costs per QALY is negligible (3%). The CEAC for QALYs indicates that the higher the willingness to pay per QALY, the lower the likelihood that MBT-DH would be preferred over S-TAU in terms of costs per QALY.

Regarding the cost-effectiveness analysis, the ICER for one additional remission with MBT-DH compared with S-TAU is approximately €29,000 in the base case scenario (Table 4). In the scenario where only healthcare costs are taken into account and other societal costs (e.g. productivity costs, justice resources costs) are ignored, the ICER per additional remission with MBT-DH is approximately €22,000. With multiple imputation under the MAR assumption, we attempted to reduce the impact of missing data on the representativeness of the final sample. The results under the (less likely) MCAR missing data scenario are somewhat different from the results under the MAR scenario.

On the basis of the top left panel in Figure 1, it can be observed that under the base case scenario there is a 58% likelihood that MBT-DH leads to more patients whose BPD remitted at additional societal costs compared with S-TAU. There is a 35% likelihood that MBT-DH dominates S-TAU, which means that it leads to more remissions at lower societal costs per patient. The

TABLE 4. Cost, Remitted Patients, QALYs and ICERs Between Baseline and 36 Months After Baseline

	MBT-DH (n = 54)			S-TAU (n = 41)			ICER	
Perspective/analysis	**Costs**	**Remitted**	**QALYs**	**Costs**	**Remitted**	**QALYs**	**€ per remission**	**€ per QALY**
Societal, MAR (base case)	€64,132	33%	1.29	€60,505	20%	1.49	€29,314	Dominated
Societal, MCAR	€58,316	37%	1.38	€55,353	23%	1.57	€26,122	Dominated
Health care sector, MAR	€61,222	33%	1.29	€58,670	20%	1.49	€22,106	Dominated

Note. This table presents mean costs, mean effects, and median incremental cost-effectiveness ratios (ICERs) for MBT-DH versus S-TAU from three different analytical perspectives. The base case scenario of this economic evaluation is performed from the societal perspective, using the data imputed under the MAR assumption. For the societal, MCAR analysis, missing data were imputed under the missing completely at random (MCAR) assumption. In the health care sector analysis (using the data imputed under the MAR assumption), BPD care costs (MBT-DH or S-TAU), medication costs, and all other health care costs besides MBT-DH or S-TAU were included. All results are based on analyses performed after bootstrapping.

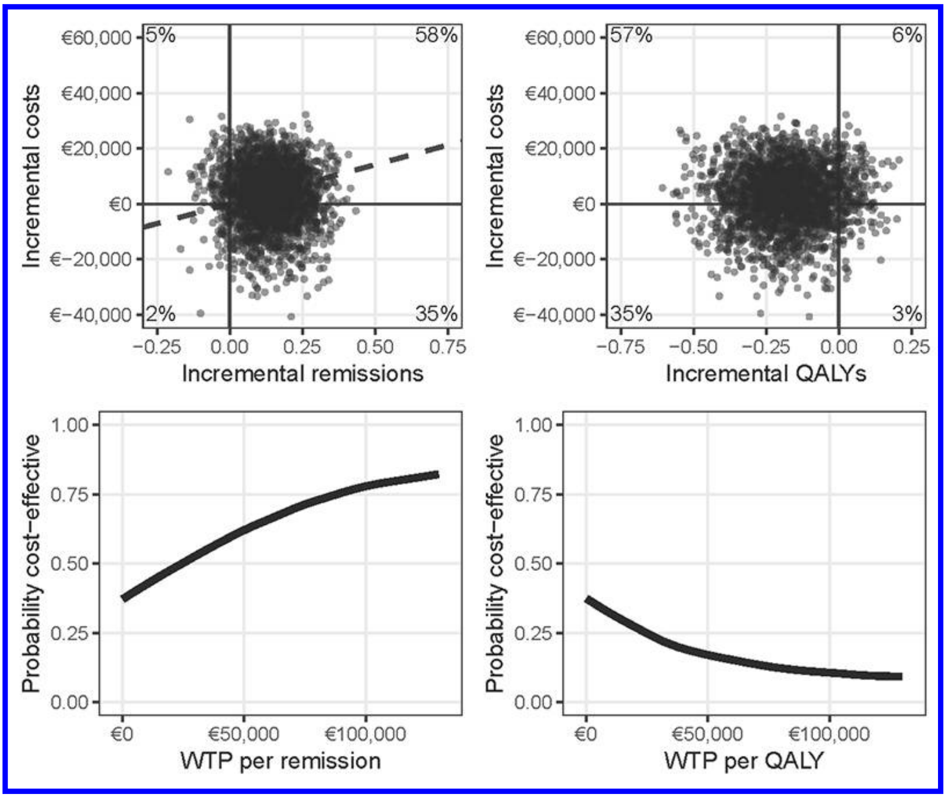

FIGURE 1. Cost-effectiveness planes and cost-effectiveness acceptability curves. The two graphs at the top of this figure are cost-effectiveness planes. In these planes, the horizontal axis indicates differences in health gains between MTD-DH and S-TAU over 36 months, while the vertical axis represents differences in costs. The chart area is divided into quadrants, each with a specific interpretation. ICERs that fall into the upper right ("northeast") quadrant indicate that MBT-DH generated better health at additional costs; the lower left ("southwest") quadrant indicates less health gains for MBT-DH than S-TAU at lower costs. In the upper left ("northwest") quadrant, MBT-DH is dominated by S-TAU, because fewer health gains are obtained at higher costs for MBT-DH compared with S-TAU. In the lower right ("southeast") quadrant, MBT-DH dominates S-TAU with more health gains at lower costs. The two plots at the bottom of this figure present cost-effectiveness acceptability curves. These curves show the probability that MBT-DH is more cost-effective than S-TAU as a function of the willingness to pay (WTP) for one additional unit of effect (one additional QALY or one additional person whose BPD remitted). The probability 0.50 on the vertical axis indicates the point of indifference. Above this indifference point, MBT-DH has a better likelihood of being preferred over S-TAU with regard to cost-effectiveness (with a likelihood equal to the probability on the vertical axis). Because the WTP per unit of effect is generally an unknown quantity, it is presented as a series of increments on the horizontal axis.

likelihood that MBT-DH is dominated by S-TAU (fewer remissions at higher costs) is almost negligible at 5%. Based on the CEAC, assuming that there is no willingness to pay more for extra remissions than in the current situation under S-TAU, there may be a preference for S-TAU (63%), while at a willingness to pay of €45,000 extra over a period of 36 months for one extra remitted patient, there is a small preference (55%) for MBT-DH.

SENSITIVITY ANALYSES

Figure 2 presents the results for the sensitivity scenarios, in order to assess the stability of the results under incorrect specification of the cost drivers of

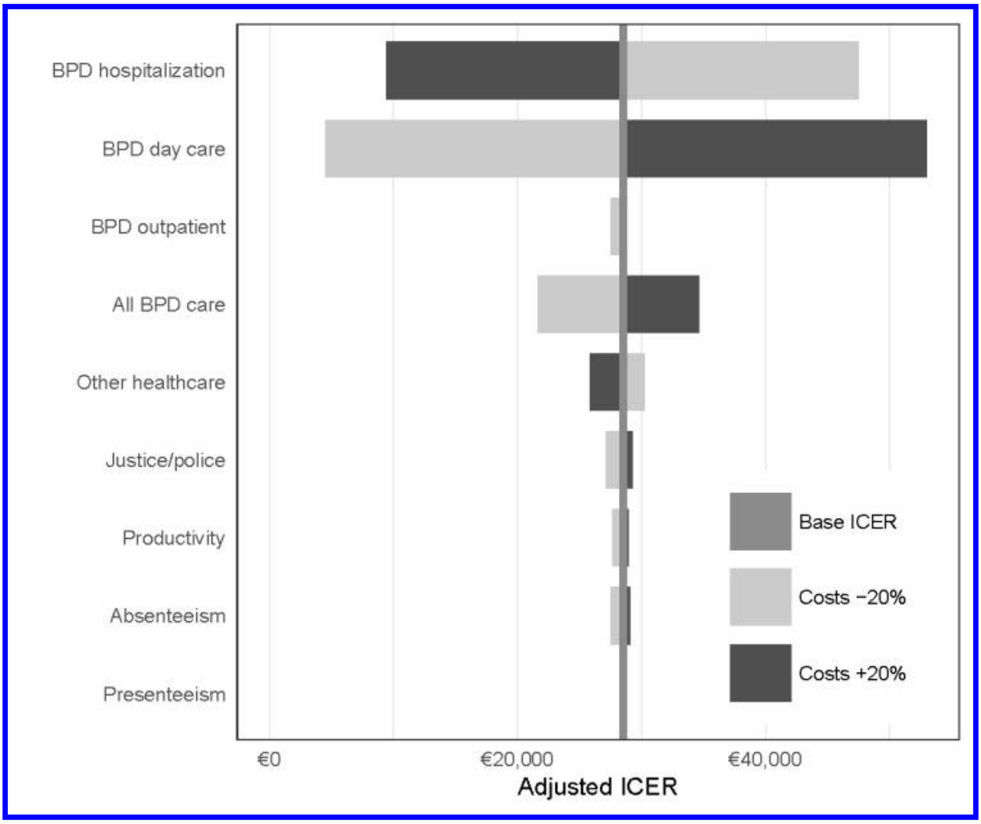

FIGURE 2. Tornado plot for the main cost drivers of the base case model for remissions. This plot indicates what the ICER with remission as an outcome would have been if the cost drivers presented on the vertical axis had been 20% higher or 20% lower than in the base case analysis. The ICER in the base case scenario is close to €29,000, as indicated by the vertical gray line that has a cross-section with the horizontal axis near that value. The cost model is sensitive to a misspecification in either BPD hospitalization costs or BPD day care costs, but not as sensitive to a misspecification of all BPD care costs simultaneously, or to any of the other cost categories.

the model. The plot indicates what the ICER with remission as an outcome would have been if the cost drivers on the vertical axis had been 20% higher or 20% lower than in the base case scenario. If BPD hospitalization costs were 20% higher or BPD day care costs were 20% lower than were assumed in our base case model, the ICER would have been lower and MBT-DH would have been more attractive in terms of costs per remission. If BPD hospitalization costs were 20% lower or BPD day care costs were 20% higher than assumed in our base case model, the opposite would have been true, and S-TAU would have been more attractive. All other cost drivers had limited impact on the incremental costs per remission.

DISCUSSION

In this article, we have evaluated the cost-utility and cost-effectiveness of MBT-DH compared with S-TAU among BPD patients. Key findings are that MBT-DH is dominated by S-TAU with QALYs as the outcome, while MBT-DH is potentially cost-effective compared with S-TAU with remissions as the outcome. The median incremental cost per incremental remission (€29,000 over 36 months, or almost €10,000 per year) is somewhat lower than the estimated costs to society of a patient with unremitted BPD (approximately €15,000 per year; see Soeteman, Hakkaart-van Roijen, et al., 2008; Laurenssen et al., 2016). At a willingness to pay of €45,000 over a 36-month period for a remitted patient, there is a 55% likelihood that MBT-DH is the more cost-effective of the two interventions, and hence a 45% likelihood that S-TAU is the more cost-effective. Although the numerical results varied, the negative results for MBT-DH in the cost-utility outcome and the favourable results in the cost-effectiveness outcome remained stable under the alternative scenarios and in sensitivity analyses.

The finding that MBT-DH was slightly superior to S-TAU in terms of cost-effectiveness with remissions as the outcome may seem out of line with the clinical results of the comparison between MBT-DH and S-TAU by Laurenssen et al. (2018). In that study, both MBT-DH and S-TAU showed significant improvements on all outcome measures at 18-month follow-up, but MBT-DH was not superior to S-TAU. The difference between the present cost-effectiveness study and the effectiveness study of Laurenssen et al. (2018) is that in the present study effects are measured over a 36-month follow-up, while Laurenssen et al. reported on only the first 18 months of follow-up. A number of studies have found that MBT can be more effective after a long period than a short period of follow-up (see, e.g., Bateman & Fonagy, 1999, 2001, 2008, 2009; Smits et al., 2019).

The finding that remission and QALY outcomes did not correspond was unexpected, especially because Cramer, Torgersen, and Kringlen (2007) showed that personality disorders in general and BPD traits are negative determinants of quality of life. However, a similar discrepancy was reported in an economic evaluation of schema-focused therapy versus transference-focused psychotherapy for BPD patients being treated in an outpatient setting using the EQ-5D-3L (van Asselt et al., 2008). These authors discussed their findings in the context of a potential difference in responsiveness of the EQ-5D and the BPDSI, but in a subsequent article they showed that the EQ-5D is fairly responsive in BPD (van Asselt, Dirksen, Arntz, Giesen-Bloo, & Severens, 2009). Furthermore, Soeteman et al. (2010, 2011) used the EQ-5D in the economic evaluation of treatments for personality disorders, with consistent results.

In our study, the EQ-5D and BPDSI were only weakly correlated, with $r = 0.34$ on average over the seven time points (range: $r = 0.11$ at baseline to $r = 0.44$ at 36 months). It should be noted that correlations at baseline will always be low due to the restriction of range through the inclusion and exclusion criteria, but even at follow-up the association was weak. A further inspection of Spearman correlations between the individual EQ-5D items and the BPDSI indicated that EQ-5D Items 1 ("Problems walking about") and 4 ("Pain or discomfort") correlated poorly ($r = 0.08$ and 0.09, respectively) with the BPDSI total score, while the only psychiatry-related item, Item 5 ("Feeling anxious or depressed") correlated somewhat better ($r = 0.40$). Hence, a difference in scores between EQ-5D items and BPDSI may be caused by the fact that the former instrument seems to measure health (improvement) on multiple independent dimensions, which are not all affected equally by BPD symptoms. Another possible explanation on the divergence between BPDSI and EQ-5D-3L is that MBT-DH is more focused on the reduction of borderline symptoms than S-TAU, while S-TAU is more focused on quality-of-life–related skills via, for example, psychosocial skills and family interventions. This explanation is in line with the meta-analysis by Newton-Howes et al. (2014), as they hypothesized that a poorer response on a certain dimension is related to a lack of focus on that dimension in treatment. In addition, the Collaborative Longitudinal Personality Disorders Study (Skodol et al., 2005) and the McLean Study of Adult Development (Zanarini, Frankenburg, Hennen, Reich, & Silk, 2005) indicate that symptomatic improvement often does not lead to social and functional improvement (see also Levy, 2008).

This study has several limitations. First, there was quite substantial dropout. Although we have addressed this statistically using multiple imputation, it may still have impacted our findings due to selective dropout. Evidence of the presence of selective dropout and its influence can be found in the variations in results based on the two different imputation strategies. The differences between the results based on the two imputation strategies do not, however, lead to substantively different conclusions. Second, although the relatively long-term follow-up and seven repeated measurements made this trial especially suitable for an economic evaluation, it was not originally powered to find statistical differences in cost data. Hence, all reported findings are probabilistic in nature, with uncertainty around all parameters. In addition, the unit costs used in the analyses were obtained from costing manuals and may be different from the actual costs accrued or paid by health care organizations, insurance companies, or other stakeholders, and in other countries. Third, although the study was a multicenter RCT, we do not know to what extent the results would generalize outside the treatment contexts in which the study took place. Additional studies are needed to further support our findings and to clarify the nature of the association between the two presented outcome parameters. A fourth limitation is that MBT-DH was provided by a newly set up treatment service, and hence implementation issues may have mitigated the treatment effects of MBT-DH. Although therapists trained in MBT were highly experienced clinicians, they had almost no prior experience with MBT. By contrast, S-TAU was well established and administered by professionals with years of experience with their approach (Laurenssen et al., 2018).

Taking into consideration the limitations of this study, we found that MBT-DH is not preferred to S-TAU at 36 months with QALYs as the outcome of the cost-utility analysis, and is slightly more cost-effective than S-TAU at 36 months when the effect parameter is the likelihood of BPD remission. The fact that there may be a paradoxical impact on overall quality of life is something that indicates a need for more research, and potentially to consider add-on interventions to address aspects of quality of life that are not addressed satisfactorily by MBT-DH.

APPENDIX

DATA COMPLETENESS

The average proportion of available data in the used variables before imputation was 0.86; this average proportion was not significantly different in the MBT-DH than in the S-TAU condition, 0.88 vs. 0.83, $t(81.4) = 1.77$, $p = .08$. Table A1 presents the average proportion of available data over all variables used in the analyses for each time point, separately for MBT-DH and S-TAU. With regard to intervention adherence, MBT-DH was associated with higher treatment adherence rates in BPD patients compared to S-TAU, reflected in significantly higher early dropout rates in S-TAU (34%) versus MBT-DH (9%) (Laurenssen et al., 2018).

SOCIETAL COSTS OF MBT-DH AND S-TAU OVER TIME

From Figure A1, it can be observed that the societal costs of MBT-DH and S-TAU follow a dissimilar pattern over the 36-month follow-up period. MBT-DH societal costs peak during the first year, when the focal MBT-DH treatment phase is most intensive, and level off during follow-up. The costs associated with S-TAU show less variation over time, based on visual inspection of the data.

TABLE A1. Data Completeness Rate Over Time in MBT-DH and S-TAU

Time (months)	MBT-DH	S-TAU
Baseline	0.96	0.93
6	0.90	0.86
12	0.89	0.81
18	0.87	0.79
24	0.85	0.81
30	0.82	0.79
36	0.87	0.84
Average	0.88	0.83

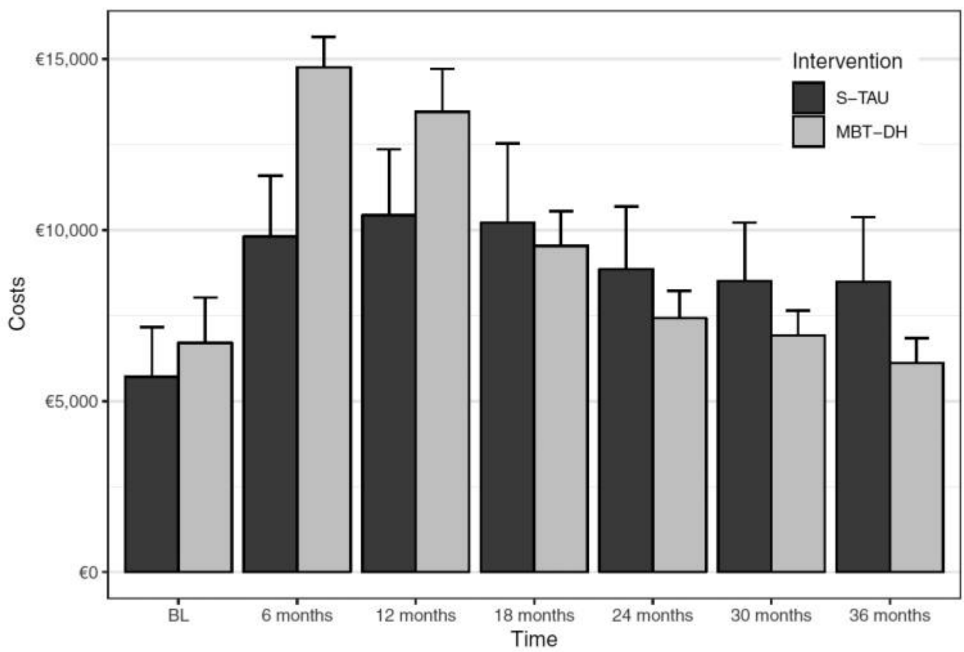

FIGURE A1. Total societal costs from baseline to 36 months. BL = baseline; MBT-DH = day hospital mentalization-based treatment; S-TAU = specialist treatment as usual.

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