ORIGINAL RESEARCH

Cost-Effectiveness of Prolonged Exposure Therapy Versus Pharmacotherapy and Treatment Choice in Posttraumatic Stress Disorder (the Optimizing PTSD Treatment Trial): A Doubly Randomized Preference Trial

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ABSTRACT

Objective: Cost-effectiveness of treatment for posttraumatic stress disorder (PTSD) may depend on type of treatment (eg, pharmacotherapy vs psychotherapy) and patient choice of treatment. We examined the cost-effectiveness of treatment with prolonged exposure therapy versus pharmacotherapy with sertraline, overall treatment preference, preference for choosing prolonged exposure therapy, and preference for choosing pharmacotherapy with sertraline from the US societal perspective.

Method: Two hundred patients aged 18 to 65 years with PTSD diagnosis based on *DSM-IV* criteria enrolled in a doubly randomized preference trial. Patients were randomized to receive their treatment of choice (n = 97) or to be randomly assigned treatment (n = 103). In the choice arm, patients chose either prolonged exposure therapy (n = 61) or pharmacotherapy with sertraline (n = 36). In the no-choice arm, patients were randomized to either prolonged exposure therapy (n = 48) or pharmacotherapy with sertraline (n = 55). The total costs, including direct medical costs, direct nonmedical costs, and indirect costs, were estimated in 2012 US dollars; and total quality-adjusted life-year (QALY) was assessed using the EuroQoL Questionnaire-5 dimensions (EQ-5D) instrument in a 12-month period. This study was conducted from July 2004 to January 2009.

Results: Relative to pharmacotherapy with sertraline, prolonged exposure therapy was less costly (–$262; 95% CI, –$5,068 to $4,946) and produced more QALYs (0.056; 95% CI, 0.014 to 0.100) when treatment was assigned, with 93.2% probability of being cost-effective at $100,000/QALY. Independently, giving a choice of treatment also yielded lower cost (–$1,826; 95% CI, –$4,634 to $749) and more QALYs (0.010; 95% CI, –0.019 to 0.044) over no choice of treatment, with 87.0% probability of cost-effectiveness at $100,000/QALY.

Conclusions: Giving PTSD patients a choice of treatment appears to be cost-effective. When choice is not possible, prolonged exposure therapy may provide a cost-effective option over pharmacotherapy with sertraline.

Trial Registration: ClinicalTrials.gov identifier: NCT00127673

Posttraumatic stress disorder (PTSD) is a chronic and debilitating condition, with lifetime prevalence rates ranging from 8%–14% of the US population.[1] Posttraumatic stress disorder also has a huge financial impact; Greenberg and colleagues[2] reported that through work impairment, hospitalization, and health visits, PTSD was more costly than any other anxiety disorder. Among the 1.64 million veterans returning from the Operation Enduring Freedom and Operation Iraqi Freedom, it is estimated that approximately 300,000 individuals currently suffer from PTSD or major depression, potentially costing $4.0 to $6.2 billion in a 2-year time frame.[3] Providing evidence-based treatment for those in need could reduce these costs by as much as 27%.[3] These considerations highlight the substantial impact of PTSD and the need for cost-effective interventions.

A significant limitation of traditional randomized clinical trials is that strong preferences for (or against) one treatment may influence outcome, willingness to receive treatment, or both.[4,5] For mental health treatments in particular, preference for treatment may moderate treatment efficacy. If preference is a moderator, then pharmacotherapy or psychotherapy may be maximally effective for those who prefer it and minimally effective for those who do not. To address this limitation in traditional randomized clinical trials, a doubly randomized preference trial design has been proposed. In a doubly randomized preference trial, participants are randomized either into a "randomization arm," within which treatment is randomized, or into a "preference arm," within which participants get to choose their treatment, thus revealing a preference for treatment. With data from a doubly randomized preference trial, the effect of choice on outcome may be separated from the effect of randomization to treatment.[5]

Preliminary and updated results from the Optimizing PTSD Treatment Trial (OPT) indicated that patients with PTSD responded well to prolonged exposure therapy or pharmacotherapy with sertraline.[6,7] In addition, there were effects on clinical outcomes for patients who received their preferred treatment.[6,7] To our knowledge, not a single study has either established methods or evaluated the cost-effectiveness of treatment preference from data derived from a doubly randomized preference trial design. In this study, we examined the cost-effectiveness of the treatment effect of prolonged exposure therapy, overall treatment preference, preference effect of choosing prolonged exposure therapy, and preference effect of choosing pharmacotherapy with sertraline from the US societal perspective.

- Giving patients a choice between prolonged exposure therapy and sertraline is a cost-effective shared decision-making strategy.

- In the absence of choice, or if the patient asks for guidance on which to choose, prolonged exposure therapy is cost-effective relative to sertraline.

- Recommending treatments that patients do not find favorable may be a barrier to successful treatment.

METHOD

Study Design and Participants

The OPT trial was a hybrid efficacy-effectiveness trial designed to compare the efficacy of prolonged exposure therapy versus pharmacotherapy with sertraline in treating PTSD and the impact of choice on both short-term and longer term outcomes. The OPT was a 2-site study conducted at the University of Washington, Seattle, and Case Western Reserve University, Cleveland, Ohio. The OPT trial included patients between ages 18 and 65 years who were currently diagnosed with primary PTSD based on the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*) criteria, with a minimum duration of 12 weeks since the traumatic event, and diagnosed using the PTSD Symptom Scale-interview version (PSS-I).[8] The study was conducted from July 2004 to January 2009. It was approved by the relevant institutional review boards, and all patients were provided written informed consent. The study was registered on ClinicalTrials.gov (identifier: NCT00127673).

Patients were randomly assigned to either choice of treatment or no choice of treatment conditions, using a doubly randomized preference trial design (Figure 1). In the choice condition, patients chose either prolonged exposure therapy or pharmacotherapy with sertraline. In the no-choice condition, patients were randomly assigned to either prolonged exposure therapy or sertraline. Patients received 10 weeks of acute treatment. All willing patients were assessed by independent evaluators at pretreatment and posttreatment and at 3-, 6-, and 12-month follow-up.

Prolonged Exposure Therapy

Patients who chose or who were randomized to prolonged exposure therapy received up to 10 weekly 90- to 120-minute treatment sessions by trained MA-, MS-, or PhD-level psychologists. As is standard, treatment procedures included education about common reactions to trauma, breathing retraining, prolonged (repeated) exposure to trauma memories, repeated in vivo exposure to situations the patient is avoiding due to trauma-related fear, and discussion of thoughts and feelings related to exposure exercises. Each session begins with a review of the homework assignment and presentation of the agenda for that session and ends with the assignment of homework utilizing a standardized prolonged exposure therapy manual.[9] Treatment sessions

were videotaped or audiotaped. Prolonged exposure therapy supervision occurred weekly at each site, including case discussion and tape review. Trained outside raters reviewed 10% of videotapes, assessing essential treatment components and protocol violations. Prolonged exposure therapy providers completed 90% of essential components. No protocol violations were observed. Prolonged exposure therapy sessions were also rated for therapist competence (eg, engaged in interactive exchange with client) on a 3-point scale (1 = inadequate, 3 = adequate or better). Overall therapist competence was very good (mean = 2.73, SD = 0.32).

Pharmacotherapy With Sertraline

Patients who chose or who were randomized to sertraline were assigned a board-certified psychiatrist throughout the study who monitored clinical state and medication effects and offered general support. Patients were seen weekly up to 30 minutes of medication management sessions for up to 10 weeks, with the first session lasting 45 minutes. The goal was to achieve a maximum target dosage of 200 mg/d of sertraline, if tolerated and indicated using a standardized titration algorithm.[10,11] Patients were assessed for response and side effects at each visit, and sertraline was also titrated to achieve the target dose. Treatment sessions were videotaped or audiotaped. The administration of sertraline was overseen by a medical director at each site. Integrity ratings were based on Marshall et al.[12] Trained raters reviewed 10% of videotapes, assessing essential treatment components and protocol violations. For essential components, pharmacotherapy with sertraline providers completed 96%. No protocol violations were observed.

Health Utility Measures

The self-administered EuroQoL Questionnaire-5 dimensions (EQ-5D)[13] was also prospectively collected to assess preference-based health-related quality of life measures of health status at pretreatment and follow-ups throughout the trial. The EQ-5D is one of the most widely used generic, preference-based, health-related quality of life measures to estimate population-based health utilities. The US population scoring system of the EQ-5D was based on the work of Shaw and colleagues.[14] In cost-effectiveness analyses, more specifically in cost-utility analyses, the standardized outcome is measured in terms of quality-adjusted life-year (QALY), which is a combined measure of quantity (in years) and quality (in population-based health utility) of life.

Health Service Utilization and Costs

All costs were based on 2012 US dollars; costs before 2012 were adjusted using the Consumer Price Index, Medical Care Service component.[15] Frequencies and durations of health service utilization was captured using the Cornell Services Index.[16] At each follow-up, patients were interviewed to answer questions about their use of outpatient (categorized into general medical health, mental health, substance abuse, and professional supportive services), inpatient, and emergency department services as well as pharmacy and

Figure 1. The Optimizing PTSD Treatment Trial Profile
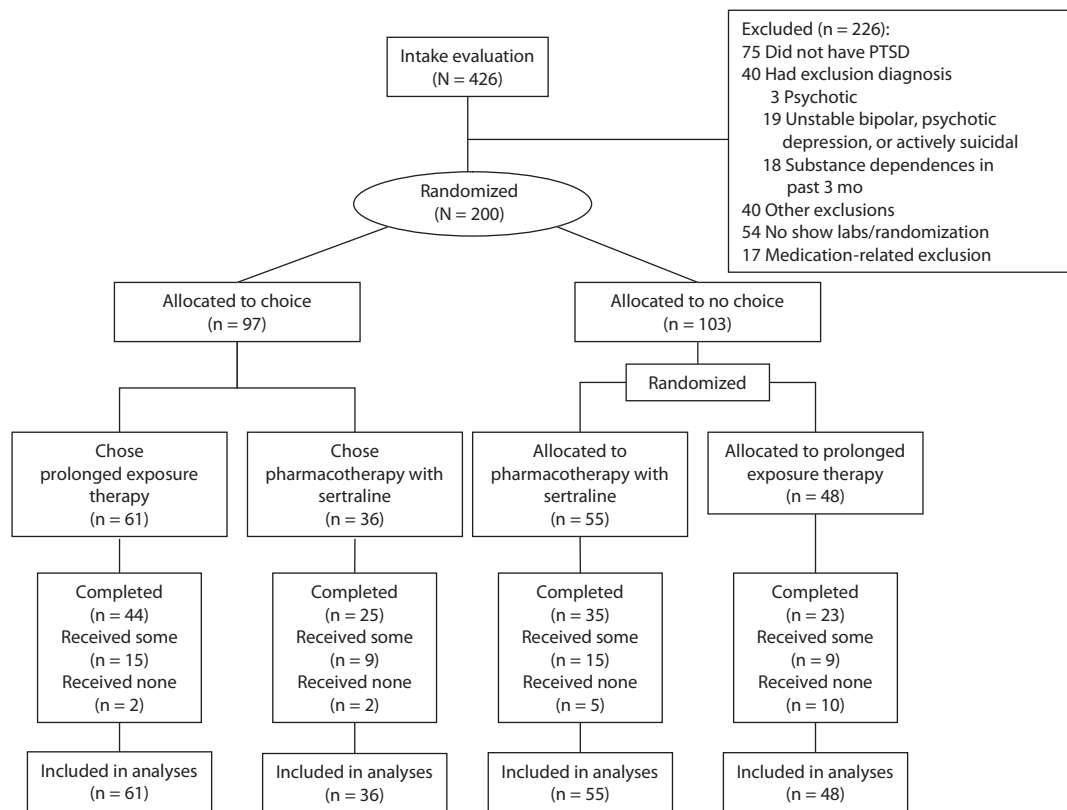
Abbreviation: PTSD = posttraumatic stress disorder.

other supportive services. We estimated the total cost per patient for each treatment arm as a sum of both direct costs (intervention costs, costs of outpatient services, inpatient hospitalization, emergency department visits, pharmacy services, and nonmedical services) and indirect cost from productivity losses.

Intervention cost in the prolonged exposure therapy arm was estimated on the basis of cost of psychologist supervisory time[17] spent for therapy sessions as well as the consulting time between and/or after treatment. In the pharmacotherapy arm, intervention cost included cost of psychiatrist supervisory time[17] for medication management and clinical consultation and cost of sertraline using its wholesale acquisition cost (WAC) from the *Drug Topics Red Book*[18] based on the total dose received during 10-week treatment. The numbers of outpatient clinic visits, inpatient hospitalizations, and emergency department visits were recorded at each follow-up. The average costs per visit for the health care services were derived from the Healthcare Cost and Utilization Project (HCUP) and Medical Expenditure Panel Survey (MEPS) statistics,[19,20] Veterans Affairs Outpatient Average Cost Dataset for VA Care,[21] and relevant published studies.[17,22] Costs of outpatient, inpatient, and emergency department visit services were estimated by multiplying the number of visit(s) by the average costs per visit. Medication use, including names of medication with their dosages, duration of use, and prescribers' information, was obtained

at each follow-up visit. Average cost of pharmacy services was estimated by using the WAC price[18] plus a pharmacy dispensing fee.[23] Cost of nonmedical services was estimated by using the self-reported commuting time to and from the clinic and time required for caregiving and/or personal home aide services with the appropriate average hourly wages from the Bureau of Labor Statistics.[17]

Indirect cost was estimated as costs of productivity losses due to time spent in weekly treatment sessions and travel time to and from the clinic multiplied by the 2012 national average wage.[17]

Statistical Analyses

All analyses were performed on an intent-to-treat approach including all 200 PTSD patients. Incremental cost-effectiveness ratios (ICERs) were estimated from the US societal perspective in a period of 12 months. The ratio was calculated as the mean difference of total cost per patient divided by the mean difference of QALY between interventions and then compared with the societal willingness-to-pay amounts for a QALY (ie, the societal valuations of expenditures for medical interventions typically between £20,000–£40,000 in the United Kingdom and $50,000–$100,000 or more in the United States[24–28]) to determine whether or not an intervention is cost-effective. We used generalized linear models to compare the estimated total costs per patient and total QALY in 12 months between interventions.[29] The models included

Table 1. Baseline Demographic and Clinical Characteristics of Patients in the Optimizing PTSD Treatment Trial[a]

	Choice Arm[b]			Randomization No-Choice Arm[c]			
Characteristic	Prolonged Exposure Therapy	Pharmacotherapy With Sertraline	Subtotal	Prolonged Exposure Therapy	Pharmacotherapy With Sertraline	Subtotal	Total
No. of patients, n (%)	61 (62.9)*	36 (37.1)*	97	55 (53.4)	48 (46.6)	103	200
Age, mean (SD), y	37.1 (11.3)	38.3 (11.4)	37.5 (11.3)	36.2 (11.4)	38.9 (11.3)	37.5 (11.4)	37.5 (11.3)
Female gender, n (%)	46 (75.4)	25 (69.4)	71 (73.2)	43 (78.2)	38 (79.2)	81 (78.6)	152 (76.0)
Education with college degree, n (%)	26 (42.6)*	8 (22.2)*	34 (35.1)	21 (38.2)	11 (23.0)	33 (32.0)	67 (33.5)
PSS-I score (PTSD severity), mean (SD)	29.1 (6.8)	30.0 (6.7)	29.5 (6.7)	29.7 (7.1)	29.6 (6.3)	29.7 (6.7)	29.6 (6.7)
Re-experiencing	7.3 (2.7)	7.5 (2.8)	7.4 (2.7)	7.8 (2.7)	7.5 (3.0)	7.7 (2.9)	7.5 (2.8)
Avoidance	12.2 (3.1)	12.4 (3.1)	12.3 (3.1)	12.3 (3.8)	11.9 (3.4)	12.1 (3.6)	12.2 (3.3)
Hyperarousal	9.6 (2.9)	10.1 (3.1)	9.8 (3.0)	9.6 (3.3)	10.2 (2.5)	9.9 (2.9)	9.8 (3.0)
CGI-S score, mean (SD)	4.6 (1.1)	4.4 (0.9)	4.5 (1.0)	4.6 (1.0)	4.5 (0.9)	4.6 (1.0)	4.6 (1.0)
EQ-5D, mean (SD)	0.65 (0.17)	0.56 (0.19)	0.62 (0.18)	0.67 (0.18)	0.60 (0.21)	0.61 (0.20)	0.63 (0.19)

[a]Patients were first randomized to either choice or no-choice arm.
[b]In the choice arm, patients chose either prolonged exposure therapy or pharmacotherapy with sertraline.
[c]In the no-choice arm, patients were randomized again to either prolonged exposure therapy or pharmacotherapy with sertraline.
*P value < .01.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, EQ-5D = EuroQoL Questionnaire-5 dimensions, PSS-I = PTSD Symptom Scale-interview version, PTSD = posttraumatic stress disorder.

demographic characteristics, baseline self-reported health status (EQ-5D), medical comorbidities, medication use, and health services utilization.

The following formula was used to estimate ICERs: ICER = ([total cost in X] – [total cost in Y])/([total QALY in X] – [total QALY in Y]).

For the treatment effect of prolonged exposure therapy as compared to pharmacotherapy with sertraline, X = patients who received prolonged exposure therapy, and Y = patients who received pharmacotherapy with sertraline.

For the overall treatment-preference effect, X = patients who were randomized to the choice arm, and Y = patients who were randomized in the no-choice or randomization arm.

For the preference effect of choosing prolonged exposure therapy, X = patients who received their preferred prolonged exposure therapy, and Y = patients who received prolonged exposure therapy but preferred pharmacotherapy with sertraline.

For the preference effect of choosing pharmacotherapy with sertraline, X = patients who received their preferred pharmacotherapy with sertraline, and Y = patients who received pharmacotherapy with sertraline but preferred prolonged exposure therapy.

Sensitivity Analyses

To quantify uncertainty around the ICERs, we examined the joint density of cost and QALY differences. In addition to base-case analyses for the most likely scenarios, we performed 1-way sensitivity analysis to test the robustness of the ICERs using the low (−25%) and high (+25%) estimates of the costs per visit for outpatient, inpatient, and emergency department services. Further, the 95% confidence intervals (CIs) for the total costs and QALYs were estimated using a nonparametric bootstrapping method with 5,000 replications.[30]

Missing Data

All missing values were imputed by using a multiple imputation method with STATA release 12.1.[31] In the imputation

models, we included 1-period lagged values of the relevant costs being imputed, demographic characteristics, baseline self-reported health status (EQ-5D), medical comorbidities, medication use, and health services utilization. We created 20 imputation data sets, and the imputation procedures were carried out separately for each intervention.

RESULTS

Table 1 briefly reports patients' demographics at baseline. In the overall sample (N = 200), patients were primarily female (76.0%), white (65.0%), middle aged (37.5 years, SD = 11.3), and not college educated (66.5%), with approximately half earning less than $20,000 per year (51.5%). In all, 31.0% reported adult sexual assault, 24.0% reported childhood assault, 22.5% reported adult assault (nonsexual assault), 13.5% reported an accident or natural disaster, 6.5% reported death of or violence to a loved one, and 2.5% reported combat or war as the primary trauma from which PTSD was assessed. The mean (SD) time elapsed since the traumatic event was 11.97 (12.69) years.

Estimated costs of health services utilization from the US societal perspective and total QALY during the 12-month period for the treatment effect of prolonged exposure therapy (prolonged exposure therapy vs pharmacotherapy with sertraline), overall effect of the treatment preference (choice of treatment vs no choice of treatment), preference effect of choosing prolonged exposure therapy, and preference effect of choosing pharmacotherapy with sertraline are presented in Tables 2 and 3.

For the treatment effect, the mean total cost of prolonged exposure therapy is slightly less than pharmacotherapy with sertraline ($7,033 vs $8,653), although this measure was not statistically significant. Similarly, for the overall effect of treatment preference, the mean total costs of both choice ($6,156) and no choice ($7,788) of treatment were not significantly different. Overall, 77.8%–86.7% of the total cost came from utilization of outpatient services, inpatient hospitalization, and emergency department visits. For the treatment effect, the QALY gain was significantly higher in the

Table 2. Unadjusted Mean Costs in 2012 US Dollars of Health Services Utilization and Total Quality-Adjusted Life-Year (QALY) in Prolonged Exposure Therapy Versus Pharmacotherapy With Sertraline (treatment effect of prolonged exposure therapy) and Choice of Treatment Versus Assignment of Treatment (overall effect of treatment preference)

Variable	Pharmacotherapy With Sertraline (n = 55)	Prolonged Exposure Therapy (n = 48)	Difference (95% CI)	No Choice of Treatment (n = 103)	Choice of Treatment (n = 97)	Difference (95% CI)
Intervention cost	$347	$457	$110 ($18 to $202)	$406	$468	$62 ($2 to –$123)
Pretreatment screening	$32	$32		$32	$32	
Sertraline	$141	$0		$65	$74	
Psychologist/psychiatrist time	$174	$425		$309	$362	
Cost of outpatient services	$3,915	$2,453	–$1,462 (–$4,204 to $1,279)	$3,134	$2,090	–$1,044 (–$2,612 to $524)
Medical services	$2,369	$1,806		$2,069	$1,390	
Mental health services	$747	$319		$518	$537	
Substance abuse treatment	$95	$91		$93	$24	
Professional support services	$709	$236		$454	$139	
Cost of inpatient hospitalization	$2,654	$2,621	–$33 (–$4,385 to $4,319)	$2,636	$1,908	–$728 (–$1,986 to $3,443)
Cost of emergency room visits	$934	$679	–$255 (–$930 to $423)	$797	$790	–$7 (–$449 to $462)
Cost of other medications	$152	$33	–$119 (–$304 to $66)	$89	$77	–$12 (–$131 to $108)
Direct nonmedical costs	$199	$122	–$77 (–$156 to $0)	$158	$195	$37 (–$26 to $99)
Transportation	$100	$94		$97	$123	
Personal home aide services	$99	$28		$61	$72	
Indirect cost (productivity losses)	$453	$669	$216 ($96 to $336)	$568	$628	$60 (–$36 to $155)
Total cost per patient per year	$8,653	$7,033	–$1,620 (–$7,262 to $4,023)	$7,788	$6,156	–$1,632 (–$5,039 to $1,774)
Total QALY per patient per year	0.726	0.823	0.096* (0.026 to 0.167)	0.778	0.771	–0.006 (–0.061 to 0.048)

*P value < .01.

Table 3. Unadjusted Mean Costs in 2012 US Dollars of Health Services Utilization and Total Quality-Adjusted Life-Year (QALY) in Receipt of the Preferred Prolonged Exposure Versus Receipt of Prolonged Exposure but Preferring Pharmacotherapy With Sertraline (preference effect of choosing prolonged exposure), and Receipt of the Preferred Pharmacotherapy With Sertraline Versus Receipt of Pharmacotherapy With Sertraline but Preferring Prolonged Exposure (preference effect of choosing pharmacotherapy with sertraline)

Variable	Received Prolonged Exposure Therapy			Received Pharmacotherapy With Sertraline		
	Preferred Pharmacotherapy With Sertraline (n = 21)	Preferred Prolonged Exposure Therapy (n = 61)	Difference (95% CI)	Preferred Prolonged Exposure Therapy (n = 30)	Preferred Pharmacotherapy With Sertraline (n = 36)	Difference (95% CI)
Intervention cost	$347	$499	$152 (–$46 to $258)	$284	$415	$131 (–$36 to $226)
Pretreatment screening	$32	$32		$32	$32	
Sertraline	$0	$0		$105	$200	
Psychologist/psychiatrist time	$315	$467		$147	$183	
Cost of outpatient services	$2,283	$2,030	–$253 (–$2,260 to $1,754)	$3,089	$2,191	–$898 (–$3,369 to $1,573)
Medical services	$1,569	$1,420		$1,789	$1,338	
Mental health services	$419	$495		$668	$610	
Substance abuse treatment	$100	$9		$40	$50	
Professional support services	$197	$107		$592	$193	
Cost of inpatient hospitalization	$5,134	$486	–$4,648 (–$9,588 to $291)	$2,396	$4,317	$1,921 (–$3,657 to $7,499)
Cost of emergency room visits	$907	$523	–$384 (–$1,186 to $419)	$993	$1,244	$251 (–$678 to $1,179)
Cost of other medications	$29	$43	$14 (–$131 to $160)	$95	$135	$40 (–$231 to $312)
Direct nonmedical costs	$121	$176	$55 (–$37 to $149)	$229	$225	–$4 (–$149 to $140)
Transportation	$96	$131		$110	$119	
Personal home aide services	$25	$45		$119	$116	
Indirect cost (productivity losses)	$620	$739	–$119 (–$39 to $306)	$475	$440	–$35 (–$180 to $108)
Total cost per patient per year	$9,441	$4,497	–$4,944 (–$10,528 to $639)	$7,561	$8,966	$1,405 (–$5,339 to $8,148)
Total QALY per patient per year	0.844	0.803	–0.040 (–0.124 to 0.043)	0.717	0.744	0.027 (–0.082 to 0.136)

prolonged exposure therapy group than the pharmacotherapy with sertraline group (95% CI of the mean QALY difference ranged from 0.026 to 0.167, P < .01) (Table 2).

For the preference effect of choosing prolonged exposure therapy, the mean total costs of patients who received their preferred prolonged exposure therapy and those who received prolonged exposure therapy but preferred pharmacotherapy with sertraline were $4,497 and $9,441, respectively. For the preference effect of choosing pharmacotherapy with sertraline, the mean total costs of patients who received their preferred pharmacotherapy with sertraline and those who received pharmacotherapy with sertraline but preferred prolonged exposure therapy were $8,966 and $7,561, respectively. Similarly, 67.6%–88.2% of the total cost came from utilization of outpatient services, inpatient hospitalization, and emergency department visits (Table 3).

Table 4. Adjusted Incremental Quality-Adjusted Life-Years (QALY); Incremental Costs for Base-Case, Low, and High Estimates[a]; and Incremental Cost-Effectiveness Ratios (ICERs) From 5,000 Bootstrap Samples

Variable	Incremental	95% CI	Incremental Cost-Effectiveness Ratio (cost/QALY)	% Bootstrap Samples Result in Cost-Effective Strategy at Willingness-to-Pay Threshold of $100,000/QALY[b]
Treatment effect of prolonged exposure therapy (prolonged exposure vs pharmacotherapy with sertraline)				
QALY	0.056*	0.014 to 0.100		
Cost				
Base case	−$262	−$5,068 to $4,946	Prolonged exposure is dominant	93.2% (prolonged exposure is cost-effective)
Low estimate	−$93	−$3,614 to $3,724	Prolonged exposure is dominant	95.3% (prolonged exposure is cost-effective)
High estimate	−$301	−$6,157 to $6,141	Prolonged exposure is dominant	91.0% (prolonged exposure is cost-effective)
Overall effect of treatment preference (choice of treatment vs no choice of treatment)				
QALY	0.010	−0.019 to 0.044		
Cost				
Base case	−$1,826	−$4,634 to $749	Choice is dominant	87.0% (choice is cost-effective)
Low estimate	−$1,274	−$3,354 to $634	Choice is dominant	84.7% (choice is cost-effective)
High estimate	−$2,239	−$5,719 to $933	Choice is dominant	88.1% (choice is cost-effective)
Preference effect of choosing prolonged exposure therapy (preferring and receiving prolonged exposure vs preferring pharmacotherapy with sertraline but receiving prolonged exposure)				
QALY	−0.048	−0.119 to 0.021		
Cost				
Base case	−$1,393	−$8,724 to $3,130	$29,021/QALY	24.4% (preferring and receiving prolonged exposure is cost-effective)
Low estimate	−$1,012	−$6,475 to $2,232	$21,083/QALY	20.2% (preferring and receiving prolonged exposure is cost-effective)
High estimate	−$1,841	−$10,952 to $3,621	$38,354/QALY	29.0% (preferring and receiving prolonged exposure is cost-effective)
Preference effect of choosing sertraline pharmacotherapy (preferring and receiving pharmacotherapy with sertraline vs preferring prolonged exposure but receiving pharmacotherapy with sertraline)				
QALY	0.027	−0.024 to 0.076		
Cost				
Base case	$714	−$5,954 to $7,661	$26,444/QALY	67.1% (preferring and receiving pharmacotherapy with sertraline is cost-effective)
Low estimate	$613	−$4,376 to $5,826	$22,704/QALY	70.9% (preferring and receiving pharmacotherapy with sertraline is cost-effective)
High estimate	$843	−$7,495 to $9,415	$31,222/QALY	64.2% (preferring and receiving pharmacotherapy with sertraline is cost-effective)

[a]Low and high estimates were based on −25% and +25% of the costs of outpatient services, inpatient hospitalizations, and emergency department visits.
[b]Percentage of bootstrap samples were observed below the willingness-to-pay amount of $100,000/QALY.
*P value < .01.

Using the base-case analyses for the most likely scenarios, low (−25%) and high (+25%) estimates of costs per visit for outpatient services, inpatient hospitalization, and emergency department visits, Table 4 reports mean incremental costs, incremental QALYs, 95% CIs, ICERs, as well as percentage of the bootstrap samples that resulted in a cost-effective strategy during a 12-month period for the treatment effect of prolonged exposure therapy, overall effect of treatment preference, preference effect of choosing prolonged exposure therapy, and preference effect of choosing pharmacotherapy with sertraline, adjusted for baseline and clinical characteristics.

For the treatment effect, prolonged exposure therapy was a dominant strategy (less costly but produced more QALYs) with the base-case analysis. The scatter plot (Figure 2A) shows that a majority of the bootstrap samples fell in the southeast quadrant, resulting in a dominant strategy for prolonged exposure therapy. At the willingness-to-pay amount of $100,000/QALY, the probability that prolonged exposure therapy is cost-effective compared with pharmacotherapy with sertraline was 93.2% (Figure 2A, Table 4).

For the overall effect of treatment preference, choice of treatment (ie, those who received the preferred treatment) was a dominant strategy with the base-case analysis. The

scatter plot (Figure 2B) also indicates that a majority of the bootstrap samples were in the dominant strategy for prolonged exposure therapy. At the willingness-to-pay amount of $100,000/QALY, the probability that choice of treatment is cost-effective compared with no choice of treatment was 87.0% (Figure 2B, Table 4).

At the base-case analysis, the preference effect of choosing prolonged exposure therapy produced less cost (incremental cost was −$1,393) and fewer QALYs (incremental QALY was −0.048), thus resulting in an ICER of $29,021/QALY for the preference effect of choosing prolonged exposure therapy (Table 4). The preference effect of choosing pharmacotherapy with sertraline yielded more cost (incremental cost was $714) and more QALYs (incremental QALY was 0.027), resulting in an ICER of $26,444/QALY for the preference effect of choosing pharmacotherapy with sertraline (Table 4). In both cases, 1-way sensitivity analyses with low- and high-estimates of costs also resulted in close estimates as in the base-case analysis.

DISCUSSION

To our knowledge, this is the first study to have evaluated not only the cost-effectiveness of the treatment effect of cognitive-behavioral therapy (CBT) versus

Figure 2. Scatter Plot of Incremental Costs in 2012 US Dollars and Incremental Quality-Adjusted Life-Years (QALYs) and Cost-Effectiveness Acceptability Curves of the (A) Treatment Effect of Prolonged Exposure Therapy Versus Pharmacotherapy With Sertraline and (B) Overall Effect of Treatment Preference in 5,000 Bootstrap Samples

(A) Prolonged Exposure Therapy Versus Pharmacotherapy With Sertraline

(B) Choice of Treatment Versus Assignment of Treatment (no choice of treatment)
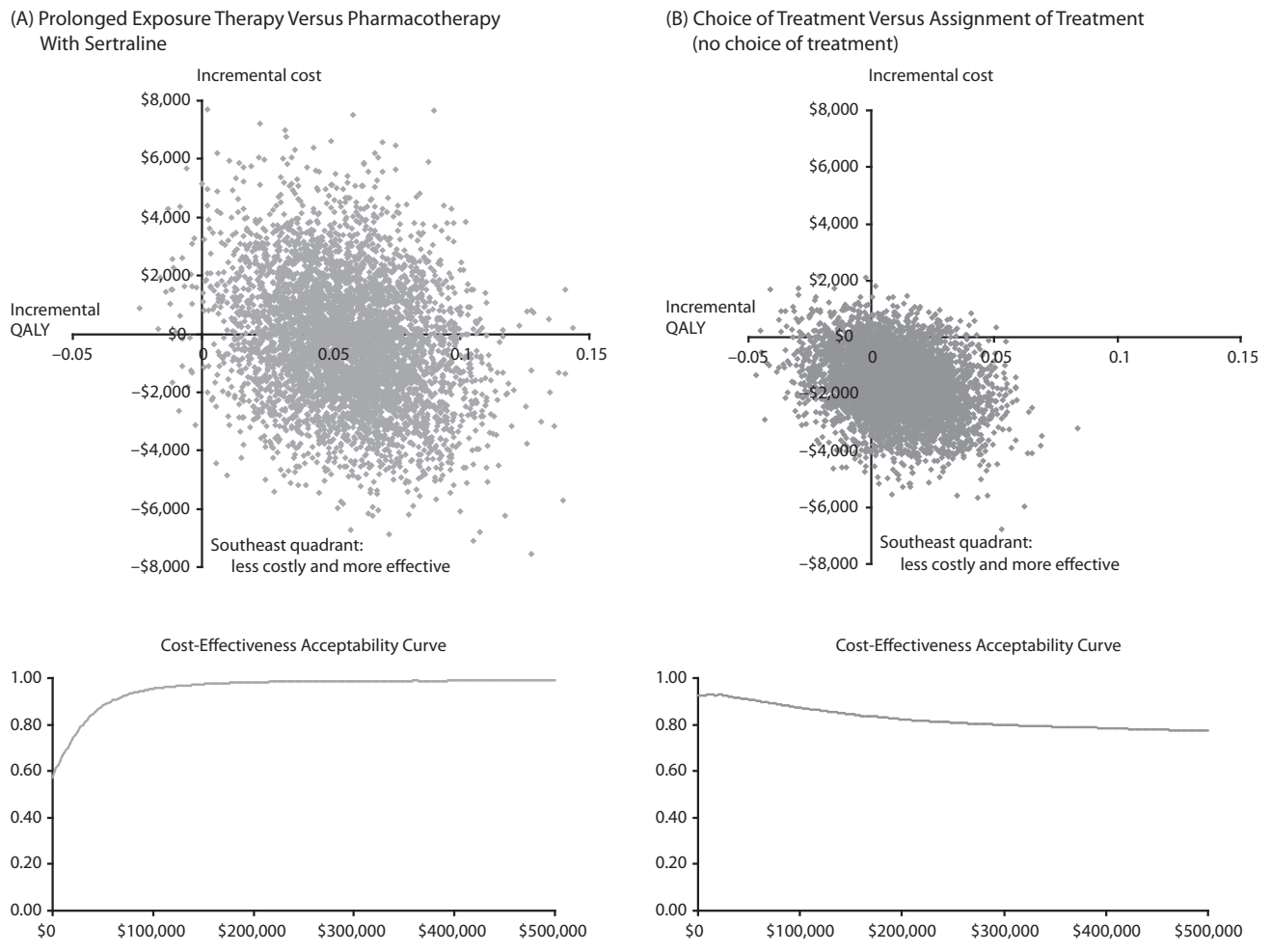
pharmacotherapy in patients with PTSD but also the cost-effectiveness of the overall treatment preference and the preference effects of choosing the preferred treatments from the US societal perspective. In general, prolonged exposure therapy and being given a choice of treatment were each more effective (produced more QALYs) at a lower cost than pharmacotherapy with sertraline and when given no choice of treatment (ie, received assigned treatment), respectively. In addition, the ICERs of patients who preferred and received prolonged exposure therapy versus those who did not prefer but received prolonged exposure therapy and of patients who received their preferred pharmacotherapy with sertraline versus those who received pharmacotherapy with sertraline but did not prefer pharmacotherapy with sertraline were $29,021/QALY and $26,444/QALY, respectively. Our study indicates that prolonged exposure therapy and receipt of preferred treatment in PTSD patients are cost-effective strategies relative to pharmacotherapy with sertraline and the receipt of assigned treatment, respectively.

Previous studies[32–35] have showed similar estimates for the average annual cost in patients with PTSD. Of the

annual total cost, the majority (67.6%–88.2%) was due to utilization of outpatient services, inpatient hospitalization, and emergency department visits. Interestingly, patients with PTSD who received prolonged exposure therapy had significantly higher health-related quality-of-life measures than those who received pharmacotherapy with sertraline. We also included the low and high estimates of major components of the total cost (outpatient services, inpatient hospitalization, and emergency department visits) in our analyses to examine the robustness of the results. Overall, the results were somewhat less sensitive to low and high cost estimates and rather consistent with the base-case analysis.

There have been few cost-effectiveness studies on treatments and/or preference treatments of PTSD. Using population-based estimates, Issakidis et al[36] found that evidence-based optimal care for PTSD (also including other anxiety disorders such as panic disorder with and without agoraphobia, social phobia, and generalized anxiety disorder) had both clinical and economic benefits against current care from the Australian health care's perspective. More recently, Gospodarevskaya and Segal[37] used Markov

models to assess the cost-effectiveness of CBT, combination of CBT and pharmacotherapy with sertraline, and nondirective counseling for treatment of PTSD in sexually abused children in Australia. This study showed that combination of CBT and sertraline was the most cost-effective therapy (ICER = 17,520 Australian dollars/QALY) in PTSD sexually abused children.[37] Joesch et al[38] examined the cost-effectiveness of treatment preference in all anxiety disorders (including panic, generalized anxiety, social anxiety, and PTSD) in terms of the Coordinated Anxiety Learning and Management (CALM) treatment model, which allows choice of treatment modality and provision of additional treatment when needed, based on a primary care effectiveness randomized controlled trial in the United States.[39] The study suggested that the CALM treatment model was cost-effective as opposed to usual care treatment in a population of patients with anxiety disorders when the willingness-to-pay amount is set at $50,000/QALY.[38] It is consistent with our findings regarding the treatment preferences for PTSD, ie, giving patients an opportunity to choose their preferred treatment tends to be more cost-effective than assigning treatment to patients. It should be noted that the CALM study was not a doubly randomized preference trial and, accordingly, is unable to support strong causal statements about costs of patient preference.

The OPT trial utilized a methodologically sound doubly randomized preference design. Randomized efficacy trials make an assumption of equipoise; that is, treatments are generally perceived as equally desirable. If this is not the case, inferences are then limited to part of the population willing to be randomized, potentially excluding an important subset.[5] Notably, for treatments that require strong motivation or effort on the part of participation (eg, prolonged exposure therapy), when randomization to such a treatment that is not desired occurs, randomization is undermined and complicates causal inferences.[5] A doubly randomized preference trial helps to address this problem and is useful in studying the causal effect of choosing treatment rather than being randomly assigned, and thus can provide important information for assessing effectiveness of an intervention under real-world conditions.

Interpretation of these findings should be done with consideration of some additional limitations. First, study patients were largely female. Therefore, the results might not generalize to the general population of patients with PTSD, the veteran population in particular, as gender might play an important role in health services utilization. Second, we relied on structured interviews and patient self-report at follow-up for most measures, which might not reflect the true costs of health services utilization as if collected directly through medical records or hospital cost accounting systems. Finally, as with large-scale clinical psychotherapy and pharmacotherapy trials, some patients did not complete treatment or had missing follow-up data. This limitation was addressed by using an intent-to-treat approach and a widely accepted multiple-imputation method.

Despite the mentioned limitations, the current study has several strengths. First, it is the first economic analysis that has examined both the treatment effect of prolonged exposure therapy compared with pharmacotherapy with sertraline and the treatment-preference effects of received preferred therapies versus received nonpreferred therapies in patients with chronic PTSD. Second, the study was based on a relatively large, diverse, and clinical complex sample from a methodologically sound doubly randomized preference trial; thus, our results would be less susceptible to potential bias or confounding. Third, we evaluated not only the point estimate results but also the uncertainty (95% CI estimation) and variation (low- and high-cost estimate analyses) in incremental costs and QALYs.

In conclusion, our findings indicate that giving patients with PTSD a choice of treatment appears to be cost-effective. When choice is not possible, prolonged exposure therapy may provide a cost-effective option as compared to pharmacotherapy with sertraline.

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