Cost-Efficacy of Individual and Combined Treatments for Panic Disorder

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Objective: The objective of this study was to examine the relative cost-efficacy of empirically supported treatments for panic disorder. As psychosocial, pharmacologic, and combined treatments have all demonstrated efficacy in the treatment of panic disorder, cost-efficacy analysis provides an additional source of information to guide clinical decision making.

Method: Cost-efficacy was examined based on results from the Multicenter Comparative Treatment Study of Panic Disorder, a randomized controlled trial of treatment for panic disorder (DSM-III-R). The trial was conducted from May 1991 to April 1998. Cost-efficacy ratios representing the cost per 1-unit improvement in Panic Disorder Severity Scale mean item score were calculated for 3 monotherapies (cognitive-behavioral therapy [CBT], imipramine, and paroxetine) and 2 combination treatments (CBT-imipramine and CBT-paroxetine) at the end of acute, maintenance, and follow-up phases.

Results: Results demonstrated consistently greater cost-efficacy for individual over combined treatments, with imipramine representing the most cost-efficacious treatment option at the completion of the acute phase (cost-efficacy ratio = $972) and CBT representing the most cost-efficacious option at the end of maintenance treatment (cost efficacy ratio = $1449) and 6 months after treatment termination (cost-efficacy ratio = $1227).

Conclusion: In the context of similar efficacy for combined treatments, but poorer cost-efficacy, current monotherapies should be considered the first-line treatment of choice for panic disorder. Additionally, CBT emerged as the most durable and cost-effective monotherapy and, hence, should be considered as a particularly valuable treatment from the perspective of cost accountability.

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Panic disorder is a disabling condition with a chronic course that is often associated with high levels of impairment,[1] as well as high health care and other related costs.[2,3] Clinical outcome studies have demonstrated efficacy for a variety of treatments for panic disorder, including cognitive-behavioral,[4–6] pharmacologic,[7–10] and combination treatments.[11–13]

Cost-efficacy analysis of empirically supported treatments provides a crucial perspective on the value of treatment in the current era of managed care, in which health care professionals must demonstrate accountability. Studies directly examining the cost-efficacy of treatment for panic disorder are few[14–16] and limited in that, to date, no studies have examined the cost-efficacy of a full course of combined cognitive-behavioral and pharmacologic treatment, and only studies examining meta-analytic data[8,17] have examined the cost-efficacy of selective serotonin reuptake inhibitors (SSRIs), the newer generation of pharmacologic treatments for panic disorder.

The meta-analytic approach to estimating cost-efficacy has demonstrated greater cost-efficacy of cognitive-behavioral therapy (CBT) and older pharmacologic agents over newer agents. Gould et al.[8] examined 43 studies of treatment for panic disorder between 1974 and 1994 and found that group CBT and imipramine were the least costly options per year ($600), followed by individual CBT ($1410), alprazolam ($1776), and fluoxetine ($1872). A more recent study of treatment for panic disor-

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der in Australia used meta-analytic and national survey data to estimate cost-efficacy.[17] The universal health care system in Australia consists of publicly funded health care through its Medicare program. Services not included in this program may require additional insurance coverage and are thus considered privately funded. The authors found the most cost-efficacious option to be publicly funded CBT, followed by imipramine, privately funded CBT, and, finally, paroxetine.

Another study of cost-efficacy examined actual costs accrued at a specialty outpatient treatment facility. Otto and colleagues[16] examined individuals receiving individual CBT, group CBT, or pharmacotherapy for panic disorder. The Clinical Global Impressions (CGI) Severity of Illness scale[18] was used as the primary outcome measure. At 4 months, the most optimal cost-benefit ratio per a 1-point improvement in CGI rating was for group CBT ($246), followed by pharmacotherapy ($447) and finally individual CBT ($565). Longer-term treatment gains were assessed at 1 year, at which time the cost-benefit ratio was still lowest for group CBT ($248); however, individual CBT ($646) demonstrated greater cost-efficacy than pharmacotherapy ($1153) at this assessment point.[16]

In this article, we examined the cost-efficacy of empirically supported treatments for panic disorder in the context of a multisite treatment efficacy study. The Multicenter Comparative Treatment Study of Panic Disorder (MCCTSPD) was a randomized controlled trial (RCT) examining the efficacy of treatments for panic disorder utilizing CBT, imipramine, and their combination.[19] Additionally, in the present study we examined costs for an equivalent course of treatment with paroxetine. Since the initiation of the MCCTSPD, the pharmacologic treatment of choice for panic disorder has changed from imipramine and other tricyclic antidepressants (TCAs) to SSRIs, such as paroxetine.[20,21]

This study is unique in that it allows cost-efficacy estimation of monotherapies as well as combined treatment strategies. The study also allows for examination of costs for acute as well as continuation and maintenance treatment phases. Notably, Mavissakalian and colleagues[15] have shown that maintenance treatment is cost-efficacious in an examination of acute versus maintenance treatment with imipramine using an estimation of costs and outcome based on a clinical decision model and the available literature. Reporting cost per quality-adjusted life years, 1-year maintenance therapy, either with a half dose ($3377) or full dose ($3361), was found to be more cost-efficacious than the 24-week acute treatment only ($3691), when estimated over 18 months.

Based on available data suggesting equal efficacy between imipramine and SSRIs,[22] but very different cost profiles, we hypothesized that comparison of these treatments would suggest cost-efficacy advantages for imipramine over paroxetine. We also hypothesized that, similar to previous studies,[16] individual CBT may not show cost advantages during the acute treatment phase, but would show advantages during the continuation period and beyond. Additionally, the combined treatments were expected to demonstrate the poorest cost-efficacy due to substantially higher costs in the absence of major offsetting efficacy advantages in the long run.[12,19]

METHOD

Study Design

The MCCTSPD examined the efficacy of 5 treatment options for panic disorder (*Diagnostic and Statistical Manual of Mental Disorders*, Third Edition-Revised [DSM-III-R] criteria), randomly assigning participants to receive combined CBT and imipramine (N = 65), combined CBT and placebo (N = 63), CBT alone (N = 77), imipramine alone (N = 83), or placebo alone (N = 24). The trial included 3 phases: a 3-month acute phase, a 6-month maintenance phase, and a 6-month no-treatment follow-up phase. The acute phase consisted of 11 sessions over 12 weeks of either CBT, medication management, or their combination. In the maintenance phase, sessions were continued monthly for 6 months prior to treatment termination. In the CBT conditions, a manualized treatment for panic disorder was administered by highly trained doctoral-level clinicians. In the medication conditions, medication management was provided by experienced psychiatrists. All study clinicians received certification in the study protocol. Ongoing supervision was conducted, and adherence was rated based on audiotaped sessions. The trial was conducted in 4 anxiety research clinics from May 1991 to April 1998. Written informed consent was obtained from each subject, and the study was approved by institutional review boards at each site. Detailed methods and primary outcome data are available elsewhere.[19] For the purpose of this analysis, treatment options that included the use of placebo were not examined.

The change in Panic Disorder Severity Scale (PDSS)[23] score was used as the primary efficacy measure. The PDSS is a 7-item clinician-administered scale that assesses frequency of panic attacks, distress during panic attacks, anticipatory anxiety, agoraphobic fear and avoidance, interoceptive fear and avoidance, impairment in work functioning, and impairment in social functioning.[23] Each item is scored on a 0–4 scale in which 0 = not present, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. Items are averaged to provide a composite score for the measure. The mean composite score then provides a clinically meaningful estimate of change. The PDSS has demonstrated good interrater reliability and has been shown to be sensitive to change over time.[23–25] The PDSS was administered by independent evaluators

who were trained to reliability and monitored throughout the study.

Treatment

The number of medical management and CBT sessions attended were calculated from patient records collected during the trial. The maximum number of medical management or CBT sessions over the course of the study was 17. The duration of CBT and medical management sessions was 50 and 30 minutes, respectively. For individuals in the combined treatments, these sessions were scheduled with separate clinicians. Medication dosing information was accrued by summing the amount of medication taken by each patient over the study periods of interest. Because efficacy data suggest equivalence of imipramine and SSRIs,[12,22] a *hypothetical* analysis of paroxetine alone and in combination with CBT was used based on the available dosing information for imipramine. Review of the literature on treatment for panic disorder with imipramine and paroxetine demonstrated similar initial doses, but different therapeutic and maximum doses as guided by the *Physicians' Desk Reference* (PDR).[26] For this analysis, the starting dose for paroxetine (10 mg) was set as equivalent to imipramine (10 mg). The maximum dose of imipramine used in the trial was 300 mg, which is consistent with the PDR.[26] The typical maximum paroxetine dose of 60 mg[26] was set as equivalent to 300 mg of imipramine in the analysis. Additionally, the therapeutic dose ranges, from 150 mg to 250 mg for imipramine[17] and 20 mg to 40 mg for paroxetine,[17,27] were equated for estimation of the paroxetine costs in the analysis.

Cost

Medicare/Medicaid reimbursement rates allow for the analysis of average national rates for tests and services based on the Centers for Medicare and Medicaid Services (CMS) system. Federal upper-limit reimbursement rates—reflecting the maximum amount of reimbursement when multiple sources of medication (i.e., generic and brand-name versions) are available—were used to estimate all costs. Prices for 2006 Medicaid reimbursement for medications at titrations used in the trial (10 mg) for both imipramine ($0.26) and paroxetine ($2.43) were obtained from the Drug Topics Red Book.[28] Likewise, rates for medical management ($57.36) and CBT ($108.86) sessions were determined based on 2006 Medicare reimbursement rates, available from CMS.[29] These session costs were added for the combined treatment ($166.22). Blood and other laboratory tests used for safety and medical monitoring purposes in the study were also included in the cost analysis based on 2006 Medicare clinical laboratory reimbursement rates. These tests included a physical examination, electrocardiogram, urinalysis, urine toxicology screen, and both baseline and follow-up blood tests. Only direct costs were examined in this analysis.

Statistical Analysis

Costs for each treatment modality were examined using a 1-way analysis of variance (ANOVA). As the follow-up phase did not include treatment, and thus no cost was accrued, the cost analysis was limited to the acute and maintenance phases. Post hoc tests were performed using the Tukey Honestly Significant Difference test with α set at .05. Cumulative costs were examined at the completion of the acute and maintenance phases. Significance tests were not performed on the hypothetical paroxetine conditions because dosing data from the imipramine conditions were used.

Cost-efficacy ratios were calculated for each treatment option by dividing the mean cost for each treatment by the mean change in composite PDSS score from the baseline score for that treatment. Thus, the ratios represent the cost per 1-unit decrease (improvement) in PDSS composite score achieved at the point of evaluation. Given that mean composite PDSS scores at baseline ranged from 1.82 to 1.88 across conditions, a mean change of 1 point represents mean improvement of 53% to 55%, which is greater than the 40% reduction needed to be a treatment responder.[19] Cost-efficacy ratios were calculated at the end of acute, maintenance, and follow-up phases.

Analyses were first conducted using both intent-to-treat and completers-only samples, with negligible differences; therefore, only results from the completers sample will be presented. Phase completers are presented with the assumption that in clinical practice, individuals dissatisfied with a particular treatment option would likely seek additional treatment options, which cannot be accounted for in this particular analysis. Additionally, as the frequency of safety and other medical monitoring tests would be lower in routine clinical practice, analyses were run both with and without those tests included, again with negligible differences in the results. In the combination treatment conditions, participants saw both a pharmacotherapist and a cognitive-behavioral therapist; hence, session costs reflect the combination of these efforts.

RESULTS

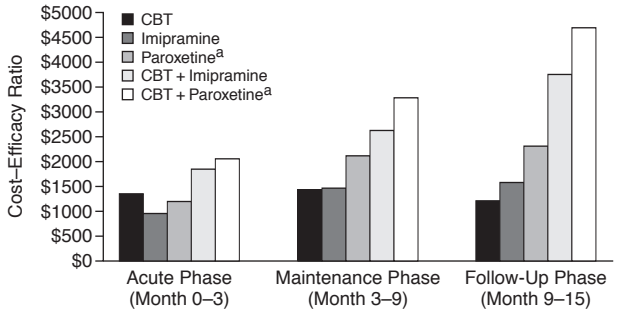
Cumulative service and total cost are presented in Table 1. Cumulative costs were presented in order to represent the entire treatment episode. In the acute phase, the mean dose of imipramine was 89 mg and in the maintenance phase, this increased to 183 mg; hence, medication costs per month were higher during the maintenance phase. Results of the ANOVA comparing costs across treatment conditions demonstrated significant between-group differences ($p < .001$) for the acute phase. Post hoc analyses in the acute phase suggested that the combined CBT-imipramine treatment had significantly

Table 1. Cumulative Mean Treatment Costs and Cost-Efficacy Ratios

Phase[a]	Treatment	Session Costs, Mean	Medication Costs, Mean	Lab Costs, Mean	Total Costs, Mean[b]	Cost-Efficacy Ratio[c]
Acute	CBT alone	$1197	$0	$0	$1197	$1369
	Pharmacotherapy alone					
	Imipramine	$630	$279	$187	$1102	$972
	Paroxetine[d]	$630	$547	$187	$1376	$1213
	Combined treatment					
	CBT + imipramine	$1802	$262	$187	$2251	$1856
	CBT + paroxetine[d]	$1802	$519	$187	$2509	$2068
Maintenance	CBT alone	$1851	$0	$0	$1851	$1449
	Pharmacotherapy alone					
	Imipramine	$975	$1220	$196	$2383	$1475
	Paroxetine[d]	$975	$2280	$196	$3445	$2132
	Combined treatment					
	CBT + imipramine	$2807	$1193	$196	$4212	$2634
	CBT + paroxetine[d]	$2807	$2244	$196	$5272	$3296
Follow-up	CBT alone	$1851	$0	$0	$1851	$1227
	Pharmacotherapy alone					
	Imipramine	$975	$1220	$196	$2383	$1596
	Paroxetine[d]	$975	$2280	$196	$3445	$2308
	Combined treatment					
	CBT + imipramine	$2807	$1193	$196	$4212	$3751
	CBT + paroxetine[d]	$2807	$2244	$196	$5272	$4694

[a]The trial included 3 phases: a 3-month acute phase, a 6-month maintenance phase, and a 6-month no-treatment follow-up phase.
[b]Total costs represent the mean total treatment cost per participant, not the sum of the means of session, medication, and laboratory costs.
[c]Cost-efficacy ratios were calculated for each treatment option by dividing the mean cost for each treatment by the mean change in composite Panic Disorder Severity Scale score from the baseline score for that treatment.
[d]Represents a *hypothetical* analysis.
Abbreviation: CBT = cognitive-behavioral therapy.

Figure 1. Cost-Efficacy Ratios for the Treatment Modalities at Completion of Each Study Phase



[a]Represents a *hypothetical* analysis.
Abbreviation: CBT = cognitive-behavioral therapy.

higher cost than both CBT alone (mean difference = $1054, $p < .001$) and imipramine alone (mean difference = $1149, $p < .001$). CBT had significantly higher cost than imipramine at this time (mean difference = $95, $p < .001$). Including paroxetine treatment, the lowest mean total cost in the acute phase was for the imipramine condition ($1102), followed by CBT ($1197), paroxetine ($1376), combination CBT-imipramine ($2251), and combination CBT-paroxetine ($2509).

Analysis of cumulative cost following the maintenance phase indicated that combined CBT-imipramine treatment again demonstrated significantly higher cost than both CBT alone (mean difference = $2361, $p < .001$) and imipramine alone (mean difference = $1829, $p < .001$). Imipramine at this time had significantly higher cost than CBT (mean difference = $532, $p < .001$). At this time, the monotherapies continued to demonstrate the lowest costs, with CBT ($1851) now the least expensive, followed by imipramine ($2383) and paroxetine ($3445). Combined CBT-imipramine ($4212) again had the lower cost of the combined treatments, and combined CBT-paroxetine condition ($5272) exceeded all other treatment options.

Figure 1 presents cost-efficacy ratios for the treatment modalities at completion of each study phase. Ratios were calculated by dividing the mean cost for each treatment by the mean change in PDSS composite score for that treatment, to arrive at a cost per 1-unit decrease in PDSS score (cost per responder). Thus, lower ratios represent more cost-efficacious options. In the acute phase, the 3 monotherapies had greater cost-efficacy than the combined treatments. Imipramine had the lowest ratio, followed by paroxetine and CBT. At the maintenance phase, the cost-efficacy of all treatment options decreased from the end of the acute phase. Following maintenance, CBT was the most cost-efficacious option, followed by imipramine, paroxetine, and the combination treatments (CBT-imipramine and CBT-paroxetine, respectively).

Six months following the termination of treatment, the monotherapies again had greater cost-efficacy than the

combined treatments. CBT continued to have the lowest cost-efficacy ratio at this time. Imipramine and paroxetine followed CBT, then CBT-imipramine and finally CBT-paroxetine. CBT was the only modality for which the cost-efficacy ratio decreased from maintenance to follow-up, suggesting greater durability of CBT over time.

DISCUSSION

This analysis examined the cost-efficacy of treatments for panic disorder based on results and patient record information from the Multicenter Collaborative Treatment Study of Panic Disorder and extended to costs for paroxetine treatment. As the paroxetine analysis is hypothetical, the results represent estimates of the cost-efficacy of paroxetine based on the available literature. Cost-efficacy ratios demonstrated advantages for monotherapies over the combined therapies at both the acute and follow-up phases. Although both pharmacologic treatments demonstrated better cost-efficacy than CBT at the end of the acute phase, CBT had the greatest cost-efficacy at both maintenance and follow-up phases with a trend suggestive of increasing cost-efficacy at follow-up. Despite similar efficacy in the imipramine and CBT conditions and higher session costs for CBT, the accrual of medication costs in the imipramine condition during the 6-month maintenance phase shifted the cost-efficacy ratio in favor of CBT. Additionally, imipramine demonstrated consistently lower cost and higher cost-efficacy than paroxetine throughout the study phases. Whereas efficacy data for imipramine has been favorable, due to a number of side effects, safety, and other issues, this medication is not typically utilized as a first-line treatment for panic disorder at this time.[20] Accordingly, SSRIs have largely replaced imipramine as the pharmacologic treatment of choice for panic disorder, and as such, the cost benefits of imipramine may not be clinically relevant.

As SSRIs such as paroxetine are beginning to become available in generic forms, the cost for these agents may decrease substantially. In order to provide an equitable method for determining the costs of services and medications, 2006 Medicare/Medicaid reimbursement rates were used to determine both visit and medication costs (i.e., lower cost sessions or medications may be available at select treatment centers or pharmacies). For example, discount pharmacies now offer paroxetine at less than our analysis price of $2.43 per pill, and, in the future, costs of SSRIs may eventually be more comparable to other generics, such as imipramine. The range of 2006 Medicare reimbursement rates for other SSRIs currently available in generic form is $0.29 to $2.43 per 10-mg pill. Hence, over time the cost-efficacy of paroxetine may begin to approximate that of imipramine if especially low-cost pills become available. Also, it should be noted that the price of the brand-name version of paroxetine is substantially higher than the Centers for Medicare and Medicaid reimbursement rates used in this analysis (26% higher according to the Drug Topics Red Book[28]), and hence the cost-efficacy is less should the brand name be used.

Cost-efficacy analysis provides an additional source of information to guide clinical decision-making, particularly when a variety of efficacious treatments are available. This information is helpful both to front-line clinicians making decisions and to policy-makers in determining the allocation of resources for both research and provision of treatment options. The literature has consistently identified CBT as the first-line treatment for panic disorder, and likewise, CBT has shown itself in this and previous studies[16] to be particularly cost-efficacious. When a full course of CBT is available, it should be considered an excellent monotherapy for patients with panic disorder, given data indicating that CBT is an especially tolerable[8] and acceptable treatment.[30] Combination treatment, in contrast, offered an especially poor cost-efficacy ratio, and hence when a CBT provider is available, the cost-efficacy data lead us to caution against the routine application of combination treatment. However, we estimated combined treatment costs by accruing cost from both CBT and pharmacotherapy providers. As an alternative to a full combination treatment, the addition of CBT strategies *within* brief pharmacotherapy sessions should provide a more cost-competitive option. This perspective is consistent with evidence from recent studies that have demonstrated that adding components of CBT (e.g., graded exposure) to medication leads to improvement in outcome at low cost.[11,31,32]

LIMITATIONS AND FUTURE DIRECTIONS

We did not include indirect costs in this analysis. Another study comparing cost-efficacy of psychosocial and pharmacologic treatments for major depression[33] found that inclusion of indirect costs continued to demonstrate cost-efficacy advantages of CBT over pharmacotherapy and combination treatments, with greater indirect costs for pharmacotherapy relative to both individual and group CBT. A focus on direct costs alone reduces the reliance on assumptions regarding costs outside of the treatment facility, although the relative cost-efficacy advantages for CBT may be attenuated by exclusion of indirect costs. Additionally, an analysis that includes a quality of life measure would have allowed for a greater understanding of the broader benefits of treatment and would be important in comparing pharmacologic and psychosocial treatments in terms of the impact of medication side effects, particularly relative to quality of life issues.

We did not directly examine cost-efficacy for SSRIs, but did complete a modeling of the results for paroxetine. These results are hypothetical, as they are based on an assumption of equivalent efficacy to imipramine. In actual

practice, the dosing and efficacy of paroxetine may differ from those that were assumed in this analysis. Although the results presented can only be interpreted as an estimate of the cost-efficacy of individual and combined treatments with paroxetine, they provide a relative comparison to the treatments utilized in the MCCTSPD study. The relative cost-efficacy reflects the likely similar efficacy, based on the available literature comparing TCAs and SSRIs for panic disorder, in the context of substantially higher cost at this time. Future research should directly examine cost-efficacy of SSRIs as they continue to represent the pharmacologic treatment of choice for panic disorder.

Another limitation regards the nature of treatment provision in the study. Both psychotherapists and pharmacotherapists were highly trained and supervised, which may reflect a higher level of care than standard clinical practice. The limitations inherent in any treatment efficacy study apply to this analysis, as it was conducted in the context of an RCT. The level of care as well as the restrictions regarding the sample treated and duration of treatment may not be fully reflective of the care provided in standard clinical practice. Additionally, the frequency of medication management visits was considerably more extensive in this RCT than in routine clinical practice. Based on a meta-analysis of 43 treatment studies and estimation of routine clinical practice, Gould et al.[8] estimated pharmacotherapy sessions to occur every other week for the first month, tapering to monthly for 3 months, and eventually occurring every third month. A review of patient charts from a specialty outpatient clinic demonstrated that the average medication management visits attended was 5.5 over the first 4 months of treatment and 13.0 over the first year.[16] This is contrasted with the sessions attended in the MCCTSPD trial of 11 in the first 3 months and 17 in the first 9 months. Furthermore, medication was discontinued after 9 months in this study, which frequently would not be done in clinical practice. We further note that most responders to acute treatment did not complete the final follow-up.[19] Completion rates ranged from 24% for imipramine to 38% for combined treatment. It is likely that at least some of those who did not complete the final follow-up remained responders, which is not accounted for in the current analysis.

The examination of cost-efficacy in the context of a RCT has been suggested to be the strongest methodology[34] but does bring with it the same potential limitations of any randomized trial.[19] A cost-effectiveness analysis in which both direct and indirect costs are assessed outside of the clinical trial environment may provide estimates of relative treatment cost-efficacy that are more generalizable to clinical practice.

Drug names: alprazolam (Xanax, Niravam, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil and others).

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