ECONOMIC ISSUES IN COMPARING ANTIDEPRESSANT DRUG THERAPY, PSYCHOTHERAPY, AND THEIR COMBINATION FOR THE TREATMENT OF ACUTE PHASE CHRONIC DEPRESSION

by

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ABSTRACT

Recently published results from a multisite randomized clinical trial demonstrate that the combination of an antidepressant pharmaceutical (nefazodone) and a particular form of psychotherapy (Cognitive Behavioral Analysis System of Psychotherapy, CBASP) achieved almost twice the remission rate than either modality alone in the treatment of acute phase chronic depression (Keller et al., 2000). Moreover, treatments involving nefazodone, by itself or in combination with CBASP, resulted in a more rapid response than CBASP alone. Combination and CBASP alone treatments, however, are typically more costly than drug therapy alone. In this paper we provide comparative cost-effectiveness assessments of these three treatment alternatives.

We employ medical and functional outcomes data (measures of symptom remission and ability to function) from the 12-week acute phase of the trial, as well as price and utilization comparison data from a medical claims database encompassing 1.4 million lives (MarketScan™, the MEDSTAT Group). The claims data are used to attribute unit costs to various clinical interventions.

Here we report findings concerning the cost-effectiveness of the three treatment alternatives. The cost comparisons employ alternative measures of outcomes (e.g., days of partial remission, days of full remission, and quality-adjusted life years), direct treatment costs, indirect treatment costs (including opportunity costs of patient time), and other economic aspects (e.g., the amortized cost of training psychotherapists the CBASP method of therapy).

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I. INTRODUCTION

Dynamic technological developments in medicine have frequently been cited as drivers of increased health care expenditures. Lewis Thomas, for example, has classified three stages in the development of medical technology.[1] In the "non-technology" phase, hospital and medical care provides little hope of recovery or improvement from the disorder, and thus treatment costs are low. The second stage is "halfway technology", in which a disorder is treated once it occurs and is diagnosed, such as with organ transplants or surgery for cancer patients. Thomas argues that halfway technology is typically very expensive. The third stage is "high technology", in which sufficient knowledge concerning the underlying disease process is gained making it possible to prevent the onset of the disorder, such as occurred with immunizations. In this third stage technology is relatively inexpensive.

The treatment of depression is still largely a halfway technology, and while we are far away from preventing its initial onset, much progress has occurred in diagnosing and treating its symptoms. Increasingly major depressive disorders (MDDs) are diagnosed and treated using psychotherapy, pharmacotherapy, or their combination.[2] Data from clinical trials generally indicate similar efficacy rates across the various generations of pharmacotherapy treatments in attaining remission of symptoms; typical response rates range from 50-60% for a first-line pharmacotherapy treatment.[3] However, the recent third and fourth generation antidepressant medications have been shown to have preferable tolerability and safety profiles relative to earlier

generation medications. By being more "user friendly", these new medications facilitate greater compliance and more effective treatment.[4] There have also been a number of important developments in the use of time-limited psychotherapy for treating MDD.[5]

Significant changes are now occurring in the way MDD is being conceptualized. Traditionally thought of as an episodic, remitting illness, MDDs are now increasingly envisaged as a chronic illness with protracted episodes or incomplete remission between episodes.[6] Epidemiological studies suggest that at any given time, about 3% of the US population suffers from chronic MDD.[7] Relative to acute MDD, chronic forms are associated with greater impairments in psychosocial function and work performance,[8] increased health care utilization,[9] and more frequent suicide attempts and hospitalizations.[10] Chronic forms of MDD account for a disproportionate share of the burden of illness associated with MDD, primarily because they frequently begin early in life and are often lifelong.[11] To the extent treatments of chronic MDD not only effectively treat a current episode, but also prevent relapse and recurrence, their value in reducing the burden of MDD could be substantial.

In the last decade the combination of pharmacotherapy and psychotherapy has been recommended in primary care practice guidelines as the treatment of choice for chronic MDD.[12] However, until recently studies investigating whether combination treatment for chronic forms of MDD is superior to mono-therapies have yielded inconclusive findings.

In a significant article recently published in the New England Journal of Medicine reporting results from a multisite twelve-week randomized clinical trial, Keller, McCullough, Klein et al. compare the combination treatment of an antidepressant pharmaceutical (nefazodone, brand name Serzone) and a particular form of psychotherapy designed specifically for chronic depression (Cognitive Behavioral Analysis System of Psychotherapy, CBASP) with mono drug and with mono CBASP treatments for chronic MDD.[13] They report that combination treatment yielded a very high therapeutic response rate (about 85% for those completing the trial), considerably greater and significantly better than that for each of the mono therapies (52-55%). Moreover, treatments involving nefazodone, by itself or in combination with CBASP, resulted in

a more rapid response than did CBASP alone.

While the very high response rate from combination therapy represents a major medical accomplishment in extending the frontier of effective treatment for patients with chronic MDD, it also raises important cost considerations. For example, in the trial the combination and CBASP treatment arms each involved between 16 and 20 sessions of psychotherapy. At current market rates, per session psychotherapy charges range between $75-$100. Mono therapy with antidepressant medications is likely to be considerably less costly, albeit also less effective. Although combination treatment is so much more effective than mono drug therapy, is the also much more costly combination treatment still comparable on a cost-effectiveness basis? How cost-effective is psychotherapy as a mono therapy? Those are the principal issues we address in this analysis.

To address issues of cost-effectiveness, we combine medical and functional outcomes data from the acute phase of the Keller, McCullough, Klein et al. trial with price and utilization comparison data from a publicly available medical claims data set encompassing 1.4 million lives (MarketScan™, from the MEDSTAT Group). The claims data provide unit costs for various interventions, which when combined with utilization data from the trial, permit us to calculate total costs of treatment.

We consider several distinct measures of outcomes (e.g., days of full remission and "depression-free days"). Our cost-effectiveness analysis incorporates not only direct medical costs, but also indirect treatment costs (including opportunity costs of patient time), and other economic aspects (e.g., indirect benefits involving reduced functional impairment).

Having piqued the curiosity of the reader, it is traditional in a paper such as this to conclude the Introduction by summarizing principal findings. In this case, however, we believe the paths taken to reach our findings are sufficiently interesting in their own right. Thus we defer any mention of findings until we first describe the trial, the way in which trial data are integrated with national medical claims data, and alternative implementations of cost-effectiveness concepts.

II. THE KELLER, MCCULLOUGH, KLEIN ET AL. CLINICAL TRIAL

A. TRIAL DESIGN, PROTOCOL AND OUTCOME MEASURES

681 outpatients from 12 academic centers were recruited between June 1996 and December 1997, each fulfilling criteria for a continuous chronic major depressive disorder of at least two years' duration. To be eligible, patients had to be between 18 and 75 years of age, and to have had a score of at least 20 on the 24-item Hamilton Rating Scale for Depression (HAMD) at initial screening, and after a two-week drug-free period, at baseline. With HAMD, higher scores indicate more severe depression. A variety of exclusion criteria were employed, most involving comorbidities such as substance abuse and mental disorders, or a recent history of non-response to previous antidepressant medication or psychotherapy treatment. Further details on patient recruitment are given in Keller, McCullough, Klein et al. [2000]. At baseline, the remaining eligible patients were randomized in a 1:1:1 ratio to receive nefazodone, psychotherapy, or a combination of nefazodone and psychotherapy.

Among those receiving nefazodone, the initial dose was 200 mg per day, which was titrated weekly in increments of 100 mg per day to a maximum of 600 mg per day, to maximize the efficacy of the drug without producing intolerable side effects. To remain in the study, by week 3 patients had to be taking at least 300 mg per day. Weekly medication management visits, each lasting 15-20 minutes, involved a psychopharmacologist checking with the patient on concomitant use of medications, and symptoms, side effects and illnesses between visits. The psychopharmacologists were not allowed to make formal psychotherapeutic interventions, such as suggesting ways to cope with stressful life events.

The CBASP treatment consisted of twice-weekly sessions during weeks 1-4, and weekly sessions during weeks 5-12. For those not adequately performing a learned social problem-solving procedure, according to clearly specified CBASP criteria, the twice-weekly CBASP sessions could be extended until week 8. Prior to the trial, trained psychotherapists (with at least two years' experience after earning an M.D. or Ph.D., or at least five years' experience after

earning an M.S.W.) attended a two-day training workshop, where their mastery of CBASP treatment procedures was certified.[14] All psychotherapy sessions conducted during the trial were videotaped, and supervisors reviewed videotapes weekly to monitor continued compliance with CBASP procedures.

The CBASP system of psychotherapy was originally developed by one of the clinical investigators, James P. McCullough, and is specifically targeted for the treatment of chronic forms of MDD, particularly to patients who had previously been "untreatable".[15] CBASP draws on a variety of behavioral, cognitive, and interpersonal techniques used in other forms of psychotherapy. It teaches patients to focus on the consequences of their behavior, and to use a social problem-solving algorithm to address interpersonal difficulties. Patients learn how their cognitive and behavioral patterns generate and perpetuate interpersonal difficulties, and then learn how to alter and remedy maladaptive patterns of interpersonal behavior. CBASP is more structured and directive than interpersonal psychotherapy,[16] and differs from cognitive therapy by focusing primarily on interpersonal interactions, including those with therapists.[17]

The primary outcomes measure was the score on the 24-item HAMD. Remission was defined as a HAMD score of no more than eight at endpoint, and at the time of withdrawal for those who did not complete the study. A less stringent outcome measure, satisfactory therapeutic response, was defined as a reduction in the HAMD score by at least 50% from baseline to endpoint. In addition, these individuals had a total HAMD score of less than 15 at endpoint or at the time of departure for those who completed the study and those who did not complete the study respectively. Patients with these favorable outcomes were combined into a group called "responders". All other patients were considered non-responders.

Of the 681 patients undergoing randomization, 226 were assigned nefazodone treatment, 228 CBASP, and 227 combined treatment. Several patients dropped out prior to attending at least one treatment, leaving a modified intent-to-treat sample of 662 (220 nefazodone, 216 CBASP, and 226 combination treatment).

B. PRINCIPAL STUDY FINDINGS

The proportion of the modified intent-to-treat sample that completed the 12-week study protocol was 78% overall, 76% for nefazodone, 80% for CBASP, and 79% for combined treatment; these differences were not significant ($p = 0.46$). The mean final daily dose of nefazodone in the intent to treat sample was 466 mg for the nefazodone group, and 460 in the combined group. Within the modified intent-to-treat sample, the mean number of psychotherapy sessions was 16.0 in the CBASP group and 16.2 in the combined group; for those who completed the study, the mean number of psychotherapy sessions was 18.2 for responders and 17.8 for non-responders.

Efficacy findings from the trial are reproduced in Table 1. As seen in the bottom panels, relative to baseline, for each of the three groups there was a significant improvement in mean HAMD scores, both at week 12 for those who completed the trial, and based on the last follow-up visit for those who did not complete the trial (p-values <0.001). The nefazodone, CBASP and combination group mean HAMD scores at week 12 (for completers) were 14.7, 15.1 and 9.7, respectively, and at the last follow-up visit were 15.8, 16.0 and 10.8. Although the difference in mean HAMD scores between nefazodone and CBASP was not statistically significant, the difference between combination and nefazodone, and between combination and CBASP, was significant (p-values < 0.001).

Rate of remission was much larger with the combination group than with either mono therapy. For those completing the 12-week trial, remission rates were 48%, 29% and 33% for the combination, nefazodone, and CBASP groups, respectively. The difference between nefazodone and CBASP, in terms of remission rates, was not significant, but each rate was significantly less than that for combination treatment (p-values <0.001). Based on the completer intent-to-treat sample, the same pattern of results emerged, although remission rates were lower. Specifically, remission rates were 42%, 22% and 24% for combination, nefazodone and CBASP treatments.

Table 1

Efficacy Data from the Keller, McCullough, Klein et al. Clinical Trial

Modified Intent to-treat Sample	(a) Nefazodone	(b) Psychotherapy	(c) Nefazodone and Psychotherapy	Pairwise p-value* a-b	a-c	b-c
No. Patients	220	216	226			
No. (%)						
Remission	64 (29)	72 (33)	109 (48)	.37	<.001	<.001
Satisfactory Response	41 (19)	31 (14)	56 (25)	.21	.10	.004
Non-Response	113 (51)	113 (52)	57 (25)			
Patients Completing the Study						
No. (%) Patients	167 (76)	173 (80)	179 (79)			
No. (%)						
Remission	36 (22)	41 (24)	75 (42)	.64	<.001	<.001
Satisfactory Response	56 (34)	49 (28)	77 (43)	.30	.07	.004
Non-Response	73 (44)	83 (48)	27 (15)			
Mean (±sd) HAMD Scores**						
Baseline	26.8±0.32	26.4±0.33	27.4±0.32			
Week 12 Completers	14.7±0.70	15.1±0.69	9.7±0.65	.68	<.001	<.001
Last Visit Response	15.8±0.64	16.0±0.63	10.8±0.63	.79	<.001	<.001

*Based on paired t-test. **Week 12 Completers and Last Visit Response HAMD scores are each significantly different from baseline for all three treatment groups (p-values <.001, based on paired t-test).

Source: Keller, McCullough, Klein et al. [2000], Tables 3 and 4.

Two aspects of these efficacy findings are worth noting. First, unlike the case of acute phase episodic depression for which placebo response rates are often in the range of 30-40%, for

chronic depressives the placebo response rate is typically much lower, about 12-15%.[18] Thus the 85% response rate to combination treatment reported in this study is extraordinary.[19]

Second, the time paths to remission and response were very different among the three groups in the trial. From baseline through week 4 of the trial, while there was no difference in the average rate of improvement in HAMD scores between the nefazodone and combination groups, these improvement rates were each greater than that for CBASP (p-values of < 0.001 for nefazodone, and 0.004 for combination therapy). From week 4 to week 12, however, the rate of improvement for nefazodone slowed and was not significantly different from that for CBASP, while the improvement rate of the combined group was significantly better than that for nefazodone ($p < 0.001$), and marginally better than that for CBASP ($p = 0.06$). By week 12, however, as seen in the bottom panel of Table 1, there was no difference in mean HAMD scores between the nefazodone and CBASP groups, although each was significantly different from that of the combined therapy group. These differences in time to response have important economic implications, as we shall discuss later in this study.

III. CONSTRUCTION AND INTERPRETATION OF HEALTH ECONOMIC OUTCOMES MEASURES

A. PATIENTS IN THE HEALTH ECONOMIC SAMPLE

In addition to clinical information, health economic data was collected at baseline and at the endpoint of the trial from patients concerning their other medical care utilization, concomitant medications, ability to function, employment status, productivity and hours worked. Since the economic information was integral to carrying out our cost-effectiveness comparisons, we conducted our health economic analysis on the subsample of patients for whom both baseline and endpoint information was available. Specifically, complete health economic data was collected for 570 of the 662 (86%) patients in the modified intent-to-treat sample. The breakdown by treatment arm is as follows: 188 of the 220 (85%) in the nefazodone group, 184 of the 216 (85%) in the CBASP group, and 198 of the 226 (88%) in the combination group. The

differences in these proportions are not statistically significant. No statistically significant differences in baseline disease severity, study diagnosis, or employment status were found between those included and those excluded from the health economic sample. The only significant difference in demographic characteristics concerned age, where differences in mean age were significant for the nefazodone (43 vs. 38) and for the combination groups (45 vs. 41), with those in the health economic analysis sample being somewhat older. We do not believe that this age difference materially biases our findings in any way. To reflect findings that are more generalizable to patients with chronic MDD, we use intent-to-treat techniques and employ the last observation carried forward.

B. ECONOMIC COST MEASURES OF DIRECT HEALTH CARE UTILIZATION

To place dollar cost values on patients' various medications and health care utilization visits, we first construct an economic analytic data file from the MEDSTAT 1997 MarketScan™ Private Pay Fee-For-Service database.[20] This data set contains health care utilization and medical claim cost data for about 1.4 million covered lives throughout the U.S., including details on diagnoses (ICD-9 codes) and medical procedures (CPT-4 codes). To obtain a comparison population group from the MarketScan data base, we selected all individuals from the 1997 data set who had a depression diagnosis (296.3x), a psychotherapy claim, and/or a nefazodone prescription drug claim. The medical claims data from these individuals are used to estimate the dollar transactions costs per unit of medical treatment. These unit cost data are the sum of the amount the third party insurer paid the provider plus any patient copayment/coinsurance. The per unit cost data are then multiplied by utilization data occurring during the trial, as recorded on patient case report forms, thereby yielding an estimate of component-specific direct medical treatment costs.

Direct medical treatment costs are the sum of six components: antidepressant pharmaceuticals, medical management, psychotherapy, diagnostic evaluations, other concomitant medications, and costs of other medical care. Each of the per unit costs are

calculated separately by geographic region (northeast, north central, south and west). We now describe each of these six components in more detail.

1. **Antidepressant Pharmaceuticals**

Total costs for nefazodone pharmaceutical treatment are calculated by multiplying the daily nefazodone doses administered during the trial (which varied over the 12-week duration of the trial) by the 1997 MarketScan nefazodone average cost per daily dose. Because of the blinded protocol in the trial, tablet dosages were not necessarily the same as would occur in the naturalistic setting. To accommodate this, we noted the daily dosage as recorded on the patient's case report form (200, 300, 350, 400, 450 and 600 mg/day), and grouping by daily dosage and goegraphic region, we calculated the average cost per day of nefazodone treatment. As seen in Table 2, although there is relatively minor variation across regions, the daily cost of nefazodone ranges from about $1.75 for 200 mg to about $3.60 for 600 mg.

2. **Medical Management**

During the trial, patients receiving nefazodone treatment had approximately weekly medical management visits with psychopharmacologists to assess tolerability, side effects and possible adverse interactions. The medication management cost per session is derived from the subset of psychologist providers responsible for medication management (CPT-4 90862) observed in the MarketScan economic analytic data file. As see near the bottom of Table 2, the unit costs for medical management ranged from $51.21 in the south to $63.30 in the northeast. The patient's total medical management costs were based on the number of visits inferred from the trial protocol dosing schedule, multiplied by the regional per unit medical management cost.

3. **Psychotherapy**

On average, patients receiving CBASP psychotherapy treatment had about 17 50-minute sessions during the trial. As seen in Table 2, the average cost for a single psychotherapy session, based on MarketScan claims coded with 40-50 minute session (CPT-4 code 90844 or 90806) with a Ph.D. or M.D. level psychotherapist, ranged from $76.01 in the west to $94.57 in the northeast. The patient's total costs for psychotherapy in the trial are calculated as the product of

the number of CBASP sessions the patient had during the trial and the regional per psychotherapy session cost.

4. **Diagnostic Evaluation Costs**

At the beginning of the trial, subjects were evaluated by a psychiatrist provider. The costs of this diagnostic evaluation were calculated using the average cost of a medical intake session by a psychiatrist provider (CPT code 90801). As seen in Table 2, this cost was about $99 for all three treatment arms.

5. **Costs of Concomitant Medications**

Costs of concomitant medications were calculated based on the concomitant medication data in the case report forms multiplied by the MarketScan derived average price.[21] As seen in Table 2, the average total cost of concomitant medications ranged from $141 for the nefazodone group, $184 for the CBASP group, and $155 for the combined group. These differences among the three groups are not statistically significant (p-values > 0.347).

6. **Costs of Other Medical Care**

The total costs of other medical care occurring during the trial were calculated based on the patients' case report forms, along with the ICD-9 diagnostic and CPT-4 procedure codes, multiplied by the MarketScan-derived average regional cost. The average of these costs was $232 per subject.

C. TIME COSTS BORNE BY PATIENTS SEEKING TREATMENT

Economic analyses of costs of medical treatment typically include estimates of patients' value of time, consistent with recommended procedures for cost-effectiveness studies.[22] Both combination and CBASP-only treatments involved approximately 17 50-minute psychotherapy sessions for each patient, along with the associated round trip travel time; for nefazodone-only and combination treatments, there was also about 11 medication management visits. That time is important to patients was recognized in the Keller, McCullough, Klein et al. New England Journal of Medicine article, where it was noted that in withdrawing their consent for

psychotherapy treatment, "11 thought treatment was too time consuming".[23]

Total time spent waiting for and receiving treatment was assumed to be 30 minutes for each medical management session, and one hour for each session of CBASP psychotherapy.[24] Patients were assumed to spend one hour traveling round trip per visit. Patients receiving combined therapy were assumed to have their medical management and CBASP psychotherapy visits on the same day, thereby requiring only one trip.

How one evaluates the opportunity cost of patient time is not without ambiguity. We proceed using two alternative computations. First, we multiply each patient's hourly wage rate with the total time in hours spent traveling, waiting for and receiving depression treatment during the trial. Patients' hourly wage rate data was obtained by using the monthly wage information collected at trial baseline, divided by the total hours worked per month. For study participants not in the labor force or for whom wage data was not reported, we used the "hotdecking" procedure to impute a wage rate. The hotdecking procedure has been used in imputing unreported data items in large national probabilistic surveys such as the Current Population Survey, which is conducted annually by the Bureau of Labor Statistics and the Census.[25] The hotdecking procedure imputes missing wage values according to gender, age group, symptom severity (HAMD) score and region, and is based on a comparison of the characteristics of the patient having missing wage information with the rest of the wage-reporting study sample population, thereby preserving the overall distribution of wages.[26]

As an alternative, we take the median wage of all patients reporting wage income in the study, and evaluate each patient's opportunity cost of time as being equal to this common median wage rate.

In either case, to obtain total time costs, we multiply the sum in hours of travel time and time spent in waiting for and receiving depression treatment, by the hourly wage rate.

D. OUTCOMES MEASURES

In contrast to the discrete outcome measures reported by Keller et al. and described above, Lave, Frank, Schulberg et al. [1998] have introduced the notion of a depression-free day (DFD), which provides a more continuous measure of health outcome. Specifically, since a HAMD score of ≤ 7 is considered symptom-free (remission) while a HAMD score of ≥ 22 indicates severe depression, Lave, Frank, Schulberg et al. assign the patient a DFD value of one if the HAMD score was ≤ 7, a value of zero if HAMD ≥ 22, and if the HAMD score is between 8 and 21, a value between zero and one equal to the proportional distance in the HAMD score between 7 and 22. We follow this procedure and calculate DFDs for each pair of time points at which the HAMD was administered, with HAMD scores on intervening days being linearly interpolated. It is worth noting that time to response in the clinical trial was more rapid for the combination and nefazodone-only groups relative to psychotherapy-alone. This differential time response will be captured by this DFD measure, whereas it is not in the standard remission and response measures. Another strength of the DFD is that it could be transformed into quality-adjusted days of life and hence be used to compute other traditional cost-effectiveness metrics such as quality of life measures (QALYs).[27]

E. OTHER INDIRECT COSTS (BENEFITS)

We envisage indirect costs as illness-related costs associated with impaired ability to function and engage in work, household, student or leisure activities. At baseline and when the patient exited the trial (usually at week 12), data on the level of impairment was collected. Specifically, based on the clinician's evaluation of the employed patient, the clinician rated the patient's level of impairment during the time specified based on a 0-100 rating scale where 0% implied no impairment (patient feels that he/she worked as much as expected by self and others, and worked at high level) and 100% implied total disability (patient feels that he/she is unable to work as a result of psychopathology). Analogous questions were asked for students and homeworkers. We interpret any reduction in impairment levels occurring during the trial as a

negative cost, or alternatively, as a benefit from treatment. Changes in impairment levels were interpreted linearly between the two points in time. To place dollar values on reduced impairment, we multiply the baseline wage rate by the interpolated percentage point difference in impairment at baseline and the given week. This latter calculation is done separately using alternatively the "hotdecking" procedure to impute missing wages, or using the median wage of all wage-reporting patients in the study as the common wage rate.

As a separate calculation, based on patients' self-reports, for those study patients who were employed, we also compute days absent from work over the previous month due to poor health. To avoid double-counting of the impairment measure, however, we do not include the absenteeism costs (or benefits) in our net total cost calculations.

F. DIRECT COSTS, INDIRECT COSTS, AND NET TOTAL COSTS

We define direct costs here as direct medical costs -- the sum of medical costs associated with antidepressant pharmaceuticals, medical management, psychotherapy, diagnostic evaluation costs, concomitant medications, other medical costs and patients' time costs for seeking care.

Whether one includes patients' time costs as direct medical costs or indirect costs is somewhat arbitrary. Although we report these time costs as a separate line item, here we include time costs as part of direct costs. The reason is that the time that patients spent in seeking care constitutes a change in patients' use of resources. Hence time costs are essentially a part of the costs for the medical intervention.[28] We calculate total indirect costs as the dollar value of reduced levels of impairment (a negative cost, or a benefit). The total indirect costs measure will therefore be negative for those responding to treatment. We define net total costs as the sum of direct costs plus indirect costs.

G. ALTERNATIVE MEASURES OF COST-EFFECTIVENESS

Based on direct costs, various measures of indirect costs, and the corresponding net total cost measures, we combine cost data with outcomes data into alternative cost-effectiveness

calculations. We present cost-effectiveness calculations based upon the remission and responder definitions used by Keller et al., and described above. However, in this paper, we place more emphasis on the depression-free day measure introduced by Lave, Frank, et al. For example, to compute net total cost per DFD for, say, the combination group we calculate the net total cost of each patient in the intent-to-treat combination therapy group, sum these up over all patients in that treatment arm, and then divide by the total number of DFDs for patients in that treatment arm. Corresponding calculations are undertaken for the other treatment arms. Notice that in each of these cost-effectiveness calculations, the costs incurred by those not responding (who continue to be depressed) are incorporated.

These cost-effectiveness measures represent average rather than incremental costs. From an economic vantage, it is of considerable interest to compute and assess incremental cost-effectiveness measures, where the increment is the effect of treatment over and above no treatment. For acute phase episodic depression, Frank, McGuire, Normand et al. [2000] have called the no treatment option "waiting list", and based on a modified two-stage expert opinion Delphi procedure involving ten psychiatric clinicians, they estimate the probability of remission from the "waiting list" option to be 15%, and the probability of a 50% improvement (analogous to "responder") as being 34%.[29]

The "waiting list" probability is likely to be less than placebo effects observed in trial, since placebo effects reflect the impact of at least clinic visits. As we noted earlier, for chronic depressives placebo effects have ranged from 12-15%, whereas for acute phase episodic depression placebo response rates typically are much higher, often ranging from 30-40%. In the absence of a expert panel Delphi procedure involving chronic depressives, similar to that by Frank, McGuire, Normand et al., we assume that the no treatment option for chronic MDD has a 12-week probability of 12% for remission, and 25% for satisfactory response.

To calculate the corresponding cost per remission (or response) accounting for the placebo effect, we compute the same cost numerator as with the average cost effectiveness measure, but then decrease the number of remitters (responders) by that proportion assumed to

have remitted (responded) had there been no treatment. We emphasize that this calculation is somewhat speculative, and should therefore be interpreted with particular caution.

IV. RESULTS

A. DIRECT, INDIRECT AND NET TOTAL COSTS; AND THEIR COMPONENTS

Table 3 reports the average total direct health care costs for patients in each of the three treatment arms, as well as the component costs. Patients treated with nefazodone had the lowest mean total direct costs ($1,930), followed by CBASP ($3,059), and combination therapy ($3,820). All pairwise comparisons of differences in mean total direct costs are statistically significant ($p<.05$).

Also indicated in Table 3 is the substantial variation in the composition of costs across the three treatment groups. Some of this variation is, of course, a function of the treatments offered in each arm of the trial. Naturally, patients in the nefazodone alone group did not have CBASP costs, just as patients in the CBASP alone group did not have nefazodone drug costs. Moreover, the combination group had the richest constellation of services by definition. However, on comparable dimensions none of the differences in the component costs is statistically significant. That is, mean drug costs for the nefazodone alone group are not significantly different from those of the combination group; the same is true of mean CBASP costs for the CBASP-alone group versus the combination group. Nor are medication management costs significantly different between the nefazodone alone and combination therapies.

Other cost components are experienced by patients in all three treatment groups. No statistically significant differences in the costs of the diagnostic intake visit or the costs of other medical care (not directly related to the trial) were found among the treatment groups. Only for time costs were any statistically significant differences found. Time costs for nefazodone alone patients in the west were found to be significantly lower than those of CBASP alone or combination therapy patients living in the west.

Table 4 reports the mean indirect costs (benefits of treatment) for each treatment group. The combination therapy group experienced the greatest benefit from improved functioning ($3,194), followed by CBASP ($2,108), and nefazodone ($1,557). Pairwise comparisons

indicate that mean indirect nefazodone costs (benefits) are not significantly smaller than those of CBASP ($p=.189$), but are smaller than those of combination therapy ($p<.001$). The mean benefit from improved functioning for CBASP patients was also smaller than that for patients receiving combination therapy ($p=.008$).

Combining total direct costs with the indirect costs yields a broad measure of net total costs that reflects both the direct costs of medical treatment and the avoided (indirect) costs associated with reduced productivity due to chronic depression that would have been incurred in the absence of treatment. In essence, these indirect costs can be interpreted as benefits--implying that the combined total cost measure can be thought of as total direct costs net of the benefits from improved functioning. This net total cost measure is reported in Table 4. Net total costs are highest for patients who received CBASP treatment alone ($963), followed by combination therapy ($626), and nefazodone treatment alone ($389). Although the differences in mean net total costs appear to be substantial, none of the pairwise comparisons across treatment arms is statistically significant due to the comparatively large within-treatment arm variation in this measure.

Before leaving this discussion of indirect and net total costs, we note that, in addition to improvements in functioning, mean absenteeism also declined on average for patients in each of the three treatment arms. At the point of their exit from the trial, patients in the nefazodone-alone and CBASP-alone groups missed about two fewer days of work in the prior month compared to their absenteeism at baseline. (On average, patients in each treatment arm reported missing about five days of work in the month prior to entering the trial.) The mean reduction in absenteeism for patients in the combination group was nearly four days. The reduction in absenteeism was not statistically different for the nefazodone-alone and CBASP-alone groups. However, the greater reduction in absenteeism for the combination therapy patients was statistically significant relative to each of the two mono therapies.

B. AVERAGE DIRECT AND NET TOTAL COST EFFECTIVENESS MEASURES

The divergence between the patterns of mean direct costs and effectiveness across the three treatment arms is a classic example of the need for cost-effectiveness analysis. As described earlier, we measure effectiveness in three primary ways--remission, response, and depression-free days (DFD). Costs are measured in two primary ways--direct medical costs and net total costs. These alternative effectiveness and cost definitions create six distinct cost effectiveness scenarios to be evaluated. The results of these cost-effectiveness calculations are reported in Table 5.

Patients receiving CBASP therapy had the highest direct cost per remission ($8,529), followed by patients receiving combination therapy ($7,004), and nefazodone alone ($5,948). Expanding the effectiveness measure to also include partial responders yields lower values for the cost effectiveness ratios because the number of patients for whom the treatments are effective increases. Direct costs per responder are highest for patients receiving CBASP therapy ($6,053), followed by patients receiving combination therapy ($4,669), and nefazodone alone ($3,779). Thus, treatment with nefazodone alone is the most cost-effective of the three therapies using either definition.

When net total costs are employed as the cost measure, the relative cost-effectiveness rankings of the three therapies are consistent whether one uses remission or response as the efficacy criterion. When the benefits from functional improvement are considered, patients receiving CBASP alone have the highest net total costs per remission ($2,684). Net total costs per remission are almost identical for the nefazodone alone and combination groups ($1,198 and $1,148, respectively). Similarly, patients receiving CBASP alone had the highest net total costs per response ($1,904), followed by combination therapy patients ($765 per responder), and nefazodone patients ($761 per responder).

Unfortunately, standard cost-effective calculations such as those just described do not permit statistical significance testing among treatment arms to be carried out because such cost-effectiveness measures are scalars. The DFD effectiveness measure presented by Lave et al. (1999), however, is continuous. Using this measure, it is possible to construct cost-effectiveness measures that contain patient-level variation. Table 5 shows the medians of direct cost per DFD

and net cost per DFD by treatment arms. Medians are presented instead of means due to the highly skewed distributions of the patient-level cost effectiveness ratios based upon both direct and net total costs. Specifically, the skewed cost distributions could be attributed to very expensive medical procedures performed during the trial period and/or a highly skewed wage distribution. As reported in Table 5, median direct treatment costs per depression free day are highest for patients receiving CBASP alone ($116), followed by combination therapy ($90), and nefazodone alone ($45). The difference in median direct treatment costs per DFD is not statistically significant for the comparison of CBASP alone and combination therapy (p=.161). However, comparisons of nefazodone alone to CBASP alone (p<.001) or combination therapy (p<.001) are statistically significant.

Similarly, median net total costs per DFD were highest for CBASP alone ($43), followed by combination therapy ($27), and nefazodone alone ($16). The difference in median costs per DFD between nefazodone alone and CBASP is statistically significant (p=.011), as is the difference between the medians for CBASP alone and combination therapy (p=.047). The difference between median total costs per DFD for nefazodone alone and combination therapy, however, is not statistically significant (p=.401).

C. SENSITIVITY ANALYSIS

We have examined the sensitivity of the results to a number of factors. First, we considered the effect of high wage earners on the indirect cost calculations. In the results presented thus far, indirect costs were valued at the patients' own wage (or imputed wage). To assess the sensitivity of the results to the wage levels of patients we also evaluated the indirect costs using the median wage of all patients as the common wage rate. Using this approach, the relative ordering of the various cost effectiveness ratios was largely unchanged. In the case of direct cost per remission, direct cost per response, net total cost per remission, and net total cost per response the relative rankings of the three treatment therapies were as follows: nefazodone-alone was the most cost-effective, followed by combination therapy, with CBASP-alone being the least cost-effective. This same ranking was preserved for net total cost per DFD. However, for total direct costs per DFD, CBASP-alone and combination therapy switched positions in terms of relative cost-effectiveness. This is because the direct cost measure does not take

account of the economic value associated with improved functional improvement of subjects in each of the three treatment arms.

We also examined the sensitivity of our findings to "waiting list" or placebo effects, which are often observed in clinical trials. As we noted earlier, for chronic depressive disorders, placebo effects have ranged from 12-15%. Hence in evaluating cost-effectiveness of treatments, we reduced the effectiveness measures in each treatment arm by the amount of the placebo effect to obtain an estimate of the actual treatment effects. Accounting for placebo effects, the treatment-induced remission rates were 46%, 28% and 30% for combination, nefazodone-alone, and CBASP-alone treatments, respectively. Correspondingly, the net costs per remission were $1,348, $1,406 and $3,163 for combination, nefazodone-alone, and CBASP-alone treatments. Note that incorporating treatment-induced measures of efficacy makes combination therapy the most cost-effective treatment, followed closely by nefazodone-alone. CBASP-alone remains the least cost-effective treatment.

In summary, CBASP-alone appears to be the least cost-effective of the three treatments for chronic depression considered here. This result is robust. Whether nefazodone-alone or combination treatment is most cost-effective varies with the efficacy criterion employed. In most cases, nefazodone appears to be the more cost-effective than combination treatment, but for net costs per remission, the two are virtually identical. Finally, when we incorporated a rough calculation for "waiting-list" or placebo response, the net cost per treatment-induced remission is slightly lower for combination treatment than for nefazodone-alone treatment.

V. IMPLICATIONS FOR THE MANAGEMENT OF DEPRESSION TREATMENTS

To our knowledge, this study represents the first comprehensive cost-effectiveness study that combines data from a prospective controlled randomized multi-center clinical trial and real-world pricing information from a large national medical claims database. The goal of this study is to assess which treatment –an antidepressant (nefazodone) alone, a specific form of psychotherapy (CBASP) alone, or their combination – is most cost-effective. The results indicate that nefazodone alone or the combination of nefazodone and CBASP are similarly cost

effective. The nefazodone-alone treatment is the least costly to deliver. However, the extraordinary clinical response with combination treatment[11] also results in significantly greater functional improvement (*i.e.*, a greater number of patients experience symptomatic remission or clinical response based upon their reduction in HAM-D scores). For patients in combination treatment, the indirect cost savings (economic benefits) from improved functional capacity offset the additional direct treatment costs for CBASP when it is combined with nefazodone.

Despite the efficacy and comparable cost-effectiveness of combination treatment with nefazodone-alone, it may be difficult for providers to rationalize treatment to all chronically depressed patients with combination treatment as first-line therapy. In particular, since treatment with combination therapy is the most expensive of the three treatment options, the cost of treatment failures would be comparatively high if combination therapy were used as first-line therapy. Moreover, since 61 patients in the trial experienced a clinical remission of their depression with nefazodone-alone, it seems plausible to argue that approximately this same number in the combination group would have responded to drug without the addition of CBASP therapy. If so, 61 of the 108 remitters in the combination group might have experienced the same clinical results without the added cost of CBASP. This raises the question as to whether the incremental costs of adding CBASP to nefazodone exceed the benefits in chronically depressed individuals that respond well to nefazodone alone. The issue of using CBASP as an augmentation strategy after 6 to 8 weeks to nefazodone non- or partial-responders may be clinically appealing and more cost-effective.

Although the current study was not designed to evaluate this cross-over or augmentation treatment strategy we are currently investigating whether it is possible to draw some inferences about the cost-effectiveness of a sequenced treatment strategy. The main complication of this analysis has to do with how individuals respond to the additional time costs associated with CBASP. As noted earlier, 11 patients withdrew from the study because of the time burden of participating in CBASP. If the addition of CBASP after 6 to 8 weeks causes some patients to discontinue nefazodone treatment, it is possible that some patients who might have responded

after a longer duration of treatment with nefazodone might not respond under the sequenced treatment approach. In general, however, it seems plausible to hypothesize that many patients who fail to respond to nefazodone alone may respond to combination therapy and relatively few patients who receive combination therapy in a sequenced approach would do worse than treatment with nefazodone alone.

VI. LIMITATIONS, FUTURE RESEARCH ISSUES, AND CONCLUDING REMARKS

In summary, combination treatment with nefazodone and CBASP resulted in the largest economic gain associated with functional improvement, which is consistent with the efficacy findings reported elsewhere. Although combination therapy was the most costly treatment alternative, surprisingly, it was nearly as cost-effective as the much less expensive nefazodone – alone treatment. This finding was largely due to the significant economic gains accompanying improved productive capacity. The results of the trial indicate that clinicians should consider antidepressant medications as an important part of their treatment of chronic depression and actively promote adjunctive psychotherapy, especially if a patient has not fully responded to medication alone.

One limitation of our study is our measure of work productivity, which is rater administered, but based on patient self-report. Some depressed individuals may overstate their baseline level of impairment. If so, the relative improvements, including the cost benefits for this improvement, may be overstated. However, our work productivity measure is highly correlated with the major clinical efficacy measure (Ham-D), as well as with the SAS-SR, and the SF-36. Studies validating this subjective measure with objective productivity measures are needed.

A number of other caveats have been evaluated extensively in sensitivity analyses reported in the results section. Issues evaluated include selection bias, alternative measures of cost and effectiveness, valuing wages at actual (or imputed) levels versus at the median wage for the entire patient population, and estimating costs with and without the valuation of time costs.

In general, these sensitivity analyses did not result in changes that altered the relative cost-effectiveness of the three alternative treatments. It is also important to note that the reported results are based upon findings from the acute phase of the trial. Maintenance phase results will be forthcoming. Finally, the limitations associated with the use of retrospective claims information and patient self-report information--both of which were central to the economic analysis--are familiar ones and should be borne in mind when interpreting the study findings.

REFERENCES

Agency for Health Care Policy Research [1999], Treatment of Depression - Newer Pharmacotherapies, Bethesda MD: AHCPR Publication No. 99-E014.

American Psychiatric Association [1993], "Practice Guidelines for Major Depressive Disorder in Adults," American Journal of Psychiatry, 150:4, Supplement, April, 1-26.

Beck, A.T., A. John Rush, B.G. Shaw and G. Emery [1979], Cognitive Therapy of Depression, New York: Guilford Press.

Berndt, Ernst R., Howard L. Bailit, Martin B. Keller, Jason C. Verner and Stan N. Finkelstein [2000], "Health Care Use and At-Work Productivity Among Employees With Mental Disorders," Health Affairs, 19:4, July/August, forthcoming.

Berndt, Ernst R., Anupa Bir, Susan H. Busch, Richard G. Frank and Sharon-Lise T. Normand [2000], "The Medical Treatment of Depression, 1991-1996: Productive Inefficiency, Expected Outcome Variations, and Price Indexes," Cambridge, MA: National Bureau of Economic Research, Working Paper, forthcoming.

Berndt, Ernst R., Susan H. Busch and Richard G. Frank [2000], "Price Indexes for Acute Phase Treatment of Depression," paper given at NBER-CRIW Conference on Medical Output and Productivity, June 12-13, 1998. Forthcoming in David Cutler and Ernst R. Berndt, eds., Medical Output and Productivity, Chicago: University of Chicago Press for the National Bureau of Economic Research.

Berndt, Ernst R., Stan N. Finkelstein, Paul E. Greenberg, Robert H. Howland, Alison Keith, A. John Rush, James Russell and Martin B. Keller [1998], "Workplace Performance Effects from Chronic Depression and Its Treatment," Journal of Health Economics, 17:5, Fall, 511-535.

Broadbent, W. Eugene., Dan G. Blazer, Linda K. George and Chiu Kit Tse [1990], "Depression, Disability Days and Days Lost from Work in a Prospective Epidemiologic Survey," Journal of the American Medical Association, 264:2524-2528.

Cameron, A. Colin and Pravin K. Trivedi [1998], Regression Analysis of Count Data, Cambridge: Cambridge University Press.

Claxton, Ami J., Anita J. Chawla and Sean Kennedy [1999], "Absenteeism Among Employees Treated for Depression," Journal of Occupational and Environmental Medicine, 41:7, July, 605-611.

Depression Guideline Panel [1993], Depression in Primary Care, Vol. 2, Rockville, MD: U.S. Department of Health and Human Services, AHCPR publication 93-0551.

Drummond, Michael F., Bernie O'Brien, Greg L. Stoddart and George W. Torrance [1997], Methods for the Economic Evaluation of Health Care Programmes, Second Edition, Oxford: Oxford University Press.

Feiger, A.D., S.D. Tarugum, M.E. Bennett, D.L. Roberts, T.T. Kensler, M.F. D'Amico, and S. A. Hardy [1998], "A Double-Blind, Placebo-Controlled Trial of Nefazodone in the Treatment of Patients Hospitalized for Major Depression," Journal of Clinical Psychiatry, 59:5, May, 246-253.

Feiger, A.D., R.J. Bielski,, J. Bremner, J.F. Heiser, Madukhar Trivedi, C.S. Wilcox, D.L. Roberts, T.T. Kensler, R.D. McQuade, S.B. Kaplita and D.G. Archibald [1999], "Double-Blind, Placebo-Substitution Study of Nefazodone in the Prevention of Relapse During Continuation Treatment of Outpatients with Major Depression," International Journal of Clinical Psychopharmacology, 14:1, 19-28.

Fortney J., K. Rost, M. Zhang, and J. Warren [1999], "The Impact of Geographic Accessibility on the Intensity and Quality of Depression Treatment," Medical Care, 37(9), 884-93.

Frank, Richard G., Ernst R. Berndt and Susan H. Busch [1999], "Price Indexes for the Treatment of Depression," in Jack E. Triplett, ed., Measuring the Prices of Medical Treatments, Washington, DC: Brookings Institution Press, 72-102.

Frank, Richard G., Susan H. Busch, and Ernst R. Berndt [1998], "Measuring Prices and Quantities of Treatments for Depression," American Economic Review, 88:2, May, 106-111.

Frank, Richard G., Thomas G. McGuire, Sharon-Lise Normand and Howard H. Goldman [1999], "The Value of Mental Health Care At The System Level: The Case of Treating Depression," Health Affairs, 18:5, September/October, 71-88.

Gold, M.R., J.E. Siegel, Louise B. Russell and Milton C. Weinstein [1996], Cost-Effectiveness in Health and Medicine, New York: Oxford University Press.

Greenberg, Paul E., Laura E. Stiglin, Stan N. Finkelstein and Ernst R. Berndt [1993a], "The Economic Burden of Depression in 1990," Journal of Clinical Psychiatry, 54:11, November, 405-418.

Greenberg, Paul E., Laura E. Stiglin, Stan N. Finkelstein and Ernst R. Berndt [1993b], "Depression: A Neglected Major Illness," Journal of Clinical Psychiatry, 54:11, November, 419-424.

Greenberg, Paul E., Ronald C. Kessler, Tara L. Nells, Stan N. Finkelstein and Ernst R. Berndt [1996], "Depression in the Workplace: An Economic Perspective," ch. 16 in J. P. Feighner and W. F. Boyers, editors, Selective Serotonin Reuptake Inhibitors, Chichester, UK: John Wiley and Sons, 327-363.

Hollon, S.D., R.J. DeRubeis, M.D. Evans, M.J. Wiemer, M.J. Garvey, W.M. Grove, and

V.B.Tuason [1992], "Cognitive Therapy and Pharmacotherapy for Depression: Singly and in Combination," Archives of General Psychiatry, 49, 774-781.

Horst, W.D. and S.H. Preskorn [1998], "Mechanism of Action and Clinical Characteristics of Three Atypical Antidepressants: Venlafaxine, Nefazodone and Buproprion," Journal of Affective Disorders, 51, 237-254.

Howland, Robert H. [1993], "Chronic Depression," Hospital Community Psychiatry, 44, 633-639.

Judd, L.L., H.S. Akiskal and M.P. Paulus [1997], "The Role and Clinical Significance of Subsyndromal Depressive Symptoms (SSD) in Unipolar Major Depression," Journal of Affective Disorders, 45, 5-18.

Kamlet, Mark S., Martcia Wade, David J. Kupfer and Ellen Frank [1992], "Cost-Utility Analysis of Maintenance Treatment for Recurrent Depression: A Theoretical Framework and Numerical Illustration," ch. 12 in Richard G. Frank and Willard G. Manning, Jr., eds., Economics and Mental Health, Baltimore: Johns Hopkins University Press, 267-291.

Keller, Martin B., D.L. Hanks and Daniel N. Klein [1996], "Summary of the DSM-IV Mood Disorders Field Trial and Issue Overview," Psychiatr Clin North Am, 19, 1-28.

Keller, Martin B., James P. McCullough, Daniel N. Klein, Bruce Arnow, David L. Dunner, Alan J. Gelenberg, John C. Markowitz, Charles B. Nemeroff, James M. Russell, Michael E. Thase, Madhukar H. Trivedi and John Zajecka [2000], "A Comparison of Nefazodone, The Cognitive Behavioral-Analysis System of Psychotherapy, and Their Combination for the Treatment of Chronic Depression," New England Journal of Medicine, 342:20, May 18, 1462-1470.

Kent, J.M. [2000], "SnaRIs, NaSSAs, and NaRIs: New Agents for the Treatment of Depression," The Lancet, 355, 911-918.

Kessler, Ronald C., Katherine A. McGonagle, Shanyang Zhao, Christopher B. Nelson, Michael Hughes, Suzann Eshlerman, Hans-Ulrich Wittchen and Kenneth S. Kendler [1994], "Lifetime and Twelve-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States: Results from the National Comorbidity Survey," Archives of General Psychiatry, 51:1, January, 8-19.

Kessler, Ronald C., Katherine A. McGonagle, Marvin Swartz, Dan G. Blazer and Christopher B. Nelson [1993], "Sex and Depression in the National Comorbidity Survey I: Lifetime Prevalence, Chronicity and Recurrence," Journal of Affective Disorders, 29:85-96.

Klein, Donald N., K.A. Norden, T. Ferro et al. [1998], "Thirty-month Naturalistic Follow-up Study of Early-onset Dysthymic Disorder: Course, Diagnostic Stability, and Prediction of Outcome," Journal of Abnormal Psychology,, 107, 338-348.

Kocsis, James H. and Daniel N. Klein, eds. [1995], Diagnosis and Treatment of Chronic Depression, New York: Guildford Press.

Klerman, G.I., Myrna M. Weissman, B.J. Rounsaville and E.S. Chevron [1984], Interpersonal Psychotherapy of Depression, New York: Basic Books.

Lave, Judith R., Richard G. Frank, HerbertC. Schulberg, Mark S. Kamlet [1998], "Cost-effectiveness of Treatments for Major Depression in Primary Care Practice," Archives of General Psychiatry, 55:7, July, 645-651.

Little RJ, DB Rubin [1987] Statistical Analysis with Missing Data. New York: John Wiley and Sons.

McCullough, James P. [1984], "Cognitive-Behavioral Analysis System of Psychotherapy: An Interactional Treatment Approach for Dysthymic Disorder," Psychiatry, 47:3, 234-250.

McCullough, James P. [1991], "Psychotherapy for Dysthymia: A Naturalistic Study of Ten Patients," Journal of Nervous and Mental Disorders, 179, 734-740.

McCullough, James P. [1996a], "Cognitive Behavior Therapy for the Chronic Depressions," manuscript prepared for the Serzone Chronic Depression Study.

McCullough, James P. [1996b], "CBT-CD Training, Pilot Studies, Certification, and Adherence Monitoring Procedures," manuscript prepared for the Serzone Chronic Depression Study.

McCullough, James P. [2000], Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy, New York: Guilford Press.

Miller, Ivan W., KLG.I. Keitner, Alan F. Schatzberg, Donald N. Klein, Michael E. Thase, A. John Rush, J.C. Markowitz, D. Schlager, Susan G. Kornstein, S.M. Davis, Wilma M. Harrison and Martin B. Keller [1998], "The Treatment of Chronic Depression, Part 3: Psychosocial Functioning Before and After Treatment with Sertraline or Imipramine," Journal of Clinical Psychiatry, 59:11, 608-617.

Rush, A. John, R. Armitage, J.C. Gillin, K.A. Yonkers, A. Winokur, H. Moldofsky, G. Vogel, S.B. Kaplita, J.B. Fleming, J. Montplaisir, M.K. Erman, B. J. Albala and R.D. McQuade [1998], "Comparative Effects of Nefazodone and Fluoxetine on Sleep in Outpatients with Major Depressive Disorder", Biological Psychiatry, 44, 3-14.

Sajatovi, M., S. DiGiovanni, M. Fuller, J. Belton, E. DeVega, S. Marqua and D. Liebling [1999], "Nefazodone Therapy in Patients with Treatment-Resistant or Treatment-Intolerant Depression and High Psychiatric Comorbidity," Clinical Therapeutics, 21:4, 733-740.

Scott, Jan [2000], "Editorial: Treatment of Chronic Depression," New England Journal of Medicine, 342:20, May 18, 1518-1520.

Thomas, Lewis [1975], The Lives of a Cell. New York: Bantam Books.

Weissman, Myrna M., P.J. Leaf, M.L. Bruce, and L. Florio [1988], "The Epidemiology of Dysthymia in Five Communities: Rates, Risks, Comorbidity and Treatment," American Journal of Psychiatry, 145, 815-819.

Whalley, Diane and Stephen P. McKenna [1995], "Measuring Quality of Life in Patients with Depression or Anxiety," Pharmacoeconomics, 8:4, 305-315.

FOOTNOTES

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[1]See Thomas [1975].
[2]See, for example, Frank, Busch and Berndt [1998], Frank, Berndt and Busch [1999], and Berndt, Busch and Frank [2000].
[3]American Psychiatric Association [1993].
[4]Depression Guideline Panel [1993], American Psychiatric Association [1993], and Agency for Health Care Policy and Research [1999].
[5]For a brief summary and references, see Scott [2000].
[6]Judd, Akiskal and Paulus [1997], Keller, Hanks and Klein [1996], and Kocsis and Klein [1995].
[7]Kessler, McGonagle, Zhao et al. [1994], and Weissman, Leaf, Bruce and Florio [1988].
[8]Miller, Keitner, Schatzberg et al. [1998].
[9]Weissman, Leaf, Bruce et al. [1988], and Howland [1993].
[10]Klein, Norden, Ferro et al. [1998].
[11]Kessler, McGonagle, Zhao et al. [1994], Kessler, McGonagle, Swartz et al. [1993], Greenberg, Stiglin, Finkelstein et al. [1993a,b], and Greenberg, Kessler, Nells et al. [1996].
[12]Depression Guideline Panel [1993].
[13]Keller, McCullough, Klein et al. [2000].
[14]McCullough [1996b].
[15]See McCullough [1984,1991,1996b,2000]
[16]Klerman, Weissman, Rounsaville et al. [1984].
[17]Beck, Rush, Shaw et al. [1979].
[18]Keller, McCullough, Klein et al. [2000], p. 1469; Scott [2000], pp. 1518-1519.
[19]A placebo treatment arm was not specified in the acute phase design of this trial, due to anticipated patient recruitment problems, and ethical concerns. Placebo treatment was carried out later on in the maintenance phase of the trial.
[20]The year 1997 corresponds with the year in which the clinical trial took place.
[21]In a limited number of cases, medication cost data were not available in the economic analytic data file. In such cases, we used the 1997 Red Book.
[22]See Gold, Siegel, Russell et al. [1996]; also see Drummond, O'Brien, Stoddart et al. [1997].
[23]Keller, McCullough, Klein et al. [2000], p. 1468.
[24] Fortney, Rost, Zhang, and Warren [1999].
[25] See, http://www.bls.census.gov/cps/bimpute.htm.
[26] See, for example, Little and Rubin [1987].
[27] See, for example, Lave, Frank, Schulberg et al. [1998].
[28] See, for example, Gold, Siegel, Russell et al. [1996], p. 180-181.
[29]Also see Berndt, Bir, Busch et al. [2000].

Table 2
Drug and Treatment Costs per Unit of Service
by treatment group

	Nefazodone Only, A (n=188)		CBASP Only, B (n=184)		Nefazodone and CBASP, C (n=198)		Total (n=570)		p-value		
Average Costs Among Users	mean/freq	sd/%	mean/freq	sd/%	mean/freq	sd/%	mean/freq	sd/%	A vs. B	B vs. C	A vs. C
Total Nefazodone tablets, study period	346.65	118.83			350.91	102.75	348.84	110.75			0.707
Total Number of Days on Nefazodone recorded by dosing schedule	83.16	21.52			84.99	17.65	84.10	19.62			0.364
Nefazodone Cost/mean daily dosage[1]	2.40	0.46			2.39	0.39	2.39	0.42			0.875
Cost by Average Dosage											
200 mg/day											
Northeast	1.79				1.79		1.79				
North Central	1.80				1.80		1.80				
South	1.73				1.73		1.73				
West	1.75				1.75		1.75				
300 mg/day											
Northeast	1.95				1.95		1.95				
North Central	1.91				1.91		1.91				
South	1.82				1.82		1.82				
West	1.93				1.93		1.93				
350 mg/day											
Northeast	2.17				2.17		2.17				
North Central	2.10				2.10		2.10				
South	2.10				2.10		2.10				
West	2.23				2.23		2.23				
400 mg/day											
Northeast	2.38				2.38		2.38				
North Central	2.30				2.30		2.30				
South	2.38				2.38		2.38				
West	2.52				2.52		2.52				
450 mg/day											
Northeast	2.48				2.48		2.48				
North Central	2.37				2.37		2.37				
South	2.40				2.40		2.40				
West	2.63				2.63		2.63				
600 mg/day											
Northeast	3.68				3.68		3.68				
North Central	3.51				3.51		3.51				
South	3.38				3.38		3.38				
West	3.87				3.87		3.87				
Psychotherapy Cost per Session[2]											
Northeast			94.57		94.57		94.57				
North Central			85.07		85.07		85.07				
South			85.40		85.40		85.40				
West			76.01		76.01		76.01				
Number of Psychotherapy Sessions			17.28	3.29	17.28	3.49	17.28	3.39		0.989	
Total Costs for Diagnostic Intake Visit	99.04	1.74	98.95	1.82	99.13	1.74	99.04	1.76	0.634	0.333	0.618
Med Mgmt Costs per Session											
Northeast	63.30				63.30		63.30				
North Central	51.87				51.87		51.87				
South	51.21				51.21		51.21				
West	56.31				56.31		56.31				
Number of Med Mgmt Sessions	11.19	4.60			10.61	3.73	7.38	6.15			0.172

Source: BMS Clinical Trial Data and 1997MarketScan® Data; The MEDSTAT Group.

1. Pricing Data Source: 1997 MarketScan® Data; The MEDSTAT Group, and 1997 Red Book.

2. Psychotherapy cost source: 1997 MarketScan Data, CPT Code 90844 45 - 50 minute session

p-value obtained using chi-squared test for categorical variables and t-test for continuous variables.

Table 3
Cumulative Direct Medical Costs

	Nefazodone Only, A (n=188)		CBASP Only, B (n=184)		Nefazodone and CBASP, C (n=198)		Total (n=570)		p-value		
	mean/freq	sd/%	mean/freq	sd/%	mean/freq	sd/%	mean/freq	sd/%	A vs. B	B vs. C	A vs. C
Total Costs for Nefazodone											
Northeast	204.64	71.98			212.01	55.58	208.38	64.08			0.488
North Central	229.37	60.40			191.73	69.75	211.37	66.37			0.180
South	211.89	59.44			211.76	49.55	211.82	54.14			0.990
West	190.66	66.13			194.68	61.98	192.67	63.76			0.767
Total Costs for Diagnostic Intake Visit	99.04	1.74	98.95	1.82	99.13	1.74	99.04	1.76	0.634	0.333	0.618
Psychotherapy Total Costs											
Northeast			1682.11	292.30	1646.69	324.65	1470.53	296.10		0.500	
North Central			1505.77	179.57	1438.49	379.42	1663.27	309.35		0.606	
South			1426.84	305.22	1465.89	275.58	1447.77	289.18		0.454	
West			1307.34	256.50	1315.78	289.35	1311.34	271.11		0.881	
Med Mgmt Total Costs											
Northeast	711.93	263.08			676.07	228.99	694.18	245.60			0.377
North Central	510.06	116.69			466.83	129.16	489.38	121.97			0.409
South	637.44	300.91			602.26	205.62	618.58	253.85			0.454
West	553.10	190.31			515.56	175.20	534.33	182.86			0.333
Total Costs of Other Med Care	283.56	2424.43	96.14	431.35	307.94	1890.57	231.53	1799.42	0.298	0.127	0.913
Concomitant Medications[1]	141.29	222.71	184.45	543.54	154.91	401.33	159.63	406.66	0.347	0.572	0.694
Costs of Other Med Care	283.56	2424.43	96.14	431.35	307.94	1890.57	231.53	1799.42	0.298	0.127	0.913
Total Traveling- and Treatment-Time Cost											
Northeast	548.79	1501.67	956.12	1722.19	909.44	1086.52	800.81	1452.89	0.139	0.850	0.097
North Central	477.40	389.81	1296.93	1828.06	602.38	602.70	767.40	1110.92	0.195	0.277	0.558
South	874.32	4488.96	1907.38	5677.72	1177.63	2203.25	1315.96	4290.90	0.282	0.361	0.644
West	267.14	329.21	720.42	845.77	861.12	1098.97	619.95	855.30	0.001	0.484	0.001
TOTAL DIRECT COSTS	1929.87	3615.95	3059.15	3523.77	3820.33	2466.82	2951.10	3317.94	0.003	0.016	<0.001

Source: BMS Clinical Trial Data and 1997MarketScan® Data; The MEDSTAT Group.
p-value obtained using chi-squared test for categorical variables and t-test for continuous variables.
* insufficient sample size or variance to determine p-value.

Table 4
Effectiveness and Indirect Cost Measures
by treatment group

	Nefazodone Only, A (n=188)	CBASP Only, B (n=184)	Nefazodone and CBASP, C (n=198)	Total (n=570)	p-value		
					A vs. B	B vs. C	A vs. C
Number of Remitters	61	66	108	235	0.486	0.001	0.001
Number of Responders	96	93	162	351			
Depression Free Days	33.11	27.80	38.94	33.42	0.020	<0.001	0.012
QALYs	274.34	264.88	284.72	274.89	0.020	<0.001	0.012
Changes in Absenteeism	-2.32	-2.38	-3.90	-2.89	0.928	0.029	0.025
Changes in Level of Impairment	-14.47	-18.97	-27.83	-20.59	0.138	0.002	<0.001
Function-Related Costs							
Absenteeism	-237.95	-210.94	-452.63	-303.94	0.753	0.007	0.028
Changes in Level of Impairment	-1557.69	-2108.05	-3194.15	-2306.78	0.189	0.008	<0.001
Total Net Costs	388.76	962.56	626.18	656.46	0.300	0.490	0.655

Source: BMS Clinical Trial data and 1997 MarketScan® Data; The MEDSTAT Group.
p-value obtained using chi-squared test for categorical variables and t-test for continuous variables.

Table 5
Cost Effectiveness Results
by treatment group

	Nefazodone Only, A (n=188)	CBASP Only, B (n=184)	Nefazodone and CBASP, C (n=198)	Total (n=570)	p-value		
					A vs. B	B vs. C	A vs. C
Direct Cost per Remission	5947.81	8528.55	7003.94	7157.98			
Direct Cost per Response	3779.34	6052.52	4669.29	1577.92			
Direct Cost per DFD*	44.64	116.03	89.85	80.82	<0.001	0.161	<0.001
Net Cost per Remission	1198.15	2683.50	1148.00	1592.26			
Net Cost per Response	761.32	1904.42	765.33	1066.04			
Net Cost per DFD*	15.59	42.67	26.95	26.50	0.011	0.047	0.401

Source: BMS Clinical Trial data and 1997 MarketScan® Data; The MEDSTAT Group.

*p-value obtained using nonparametric tests (Wilcoxon rank-sum test/Mann-Whitney U test). Medians are presented instead of means because of the highly skewed distribution of the individual cost-effectiveness ratios.