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Cost and Cost-Effectiveness of the COMBINE Study for Alcohol-Dependent Patients

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Abstract

Context—The COMBINE clinical trial recently evaluated the efficacy of medications, behavioral therapies, and their combinations for the outpatient treatment of alcohol dependence. The costs and cost-effectiveness of these combinations are unknown and of interest to clinicians and policy makers.

Objective—To evaluate the costs and cost-effectiveness of the COMBINE interventions at the end of 16 weeks of treatment.

Design, Setting, and Participants—A prospective cost and cost-effectiveness study of patients in COMBINE, a randomized controlled clinical trial (RCT) involving 1383 patients with diagnoses of primary alcohol dependence across 11 US clinical sites.

Interventions—Nine treatment arms, with 4 arms receiving medical management with 16 weeks of naltrexone (100 mg/d) or acamprosate (3 g/d), both, and/or placebo; 4 arms receiving the same options as above but delivered with combined behavioral intervention (CBI); and 1 arm receiving CBI only.

Main Outcomes Measures—Incremental cost per percentage point increase in percent days abstinent (PDA), incremental cost per patient of avoiding heavy drinking, and incremental cost per patient of achieving a good clinical outcome.

Results—Based on the mean values of cost and effectiveness, 3 interventions are cost-effective options relative to the other interventions for all three outcomes: medical management (MM) with placebo ($409 cost per patient), MM + naltrexone ($671 cost per patient), and MM + naltrexone + acamprosate ($1003 cost per patient).

Conclusions—This is only the second prospective RCT-designed cost-effectiveness study that has been performed for the treatment of alcohol dependence. Focusing just on effectiveness, MM + naltrexone + acamprosate is not significantly better than MM + naltrexone. However, looking at cost and effectiveness, MM + naltrexone + acamprosate may be a cost-effective choice, depending on whether the cost of the incremental increase in effectiveness is worth it to the decision maker.

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INTRODUCTION

Alcohol use is the third leading preventable cause of death,[1] and alcohol abuse and dependence impose significant costs to society. In 1998, the estimated social cost of alcohol abuse was $184 billion in the United States.[2] The sizeable economic and social costs of alcohol abuse and dependence have prompted considerable interest in developing interventions to ameliorate these costs and to improve patient functioning. Several behavioral interventions (e.g., Longabaugh et al.[3]) and 2 pharmacotherapies, naltrexone and acamprosate,[4,5] have been shown to be efficacious.

Based on evidence for both approaches, the COMBINE Study was designed to examine the effects of combining behavioral and pharmacotherapies for the treatment of alcohol dependence.[6–9] COMBINE was a multicenter, randomized, controlled clinical trial (RCT) sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). COMBINE was the first study to investigate whether combinations of pharmacotherapies (naltrexone and acamprosate) with medical management (MM) and a combined behavioral intervention (CBI) are superior to monotherapy in treating alcohol dependence. A total of 1383 subjects across 11 sites were randomized into 9 treatment groups between January 2001 and the end of treatment in January 2004. Eight of the treatment groups formed a 2×2×2 factorial design. All participants in these groups received MM and were randomized to receive acamprosate or matching placebo plus naltrexone or matching placebo plus either CBI or no additional behavioral therapy. The 9th treatment group received only CBI (no medication or MM). The prespecified primary analyses involved ANOVA-type tests of main effects and interactions in the 2×2×2 factorial part of the study. Pairwise comparisons between treatment groups were not prespecified analyses and were not reported in Anton et al.[10]

Results for the primary clinical outcomes from COMBINE are available in Anton et al.[10] Briefly, in the 16-week treatment period, patients receiving MM with naltrexone, CBI, or both had better drinking outcomes than those receiving MM but neither naltrexone nor CBI. The combination of naltrexone and CBI showed no incremental benefit over CBI or naltrexone alone. Acamprosate showed no evidence of efficacy, with or without CBI or naltrexone.

Because health care resources are limited, understanding the cost and cost-effectiveness of the COMBINE interventions is important to help allocate these resources efficiently. In this paper, we evaluate the cost and cost-effectiveness of COMBINE at the end of 16 weeks of treatment. The only other RCT-designed cost-effectiveness study[11] did not evaluate combinations of pharmaceutical and behavioral interventions as is done here.

METHODS

Recruitment and Randomization

Participants were recruited by advertisement and from clinical referrals. Each participant signed an informed consent approved by the institutional review board of each site, and each site was issued a certificate of confidentiality by NIAAA. Eligibility criteria included (1) alcohol dependence, determined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)[12] criteria; (2) 4 to 21 days of abstinence; and (3) more than 14 drinks (women) or 21 drinks (men) per week, with at least 2 heavy drinking days (defined as 4 drinks per day for women and 5 drinks per day for men) during a consecutive 30-day period within the 90 days prior to baseline evaluation. Exclusion criteria included (1) history of other substance abuse (other than nicotine or cannabis) by DSM-IV criteria in the last 90 days (6 months for opiate abuse) or by urine drug screen, (2) psychiatric disorder requiring

medication, or (3) unstable medical conditions (e.g., serum liver enzyme levels >3 times the upper limit of normal). Participants' median age was 44 years, 71% had at least 12 years of education, and 42% were married. Ethnic minorities comprised 23% of the sample. In the 30 days prior to randomization, 2.3% of patients were medically detoxified and 7.7% received inpatient treatment. At baseline, mean percent days abstinent (PDA) was 25.0%, and mean drinks per drinking day was 12.5.

Cost Estimation

We followed a micro-costing approach to compute the costs of COMBINE therapies from the treatment provider perspective.[13] We estimated the costs of COMBINE from the provider perspective because this perspective is most relevant to decision makers in best clinical practice. As described in Zarkin et al.,[13] we identified COMBINE activities, laboratory procedures, and medications that would be needed to implement the therapies in clinical practice (as opposed to those required to implement a clinical trial research protocol) and then estimated the cost of each of these activities, updating unit cost estimates to 2007 dollars.

The cost of each COMBINE intervention was determined as the sum of medication, labor, space, and laboratory costs for each treatment condition. We obtained pharmaceutical costs for acamprosate and naltrexone from the Federal Supply Schedule (FSS). FSS prices are negotiated by the Veterans Administration (VA) and are publicly available. These prices are based on the prices that manufacturers charge their "most-favored" non-federal customers. The FSS price of acamprosate is $0.64 per 333 mg tab, and the FSS price of naltrexone is $1.37 per 50 mg tab. This translates into a cost per day of $5.76 for acamprosate and $2.74 for naltrexone, when the naltrexone dose is fully titrated.

To estimate labor costs, we obtained the actual clinician time spent on MM and CBI from the data coordinating center's data management system (DMS). These data were collected prospectively as part of COMBINE. Salary data (including fringe) for all staff involved in COMBINE interventions were obtained from the cost-effectiveness principal investigators (PIs) at each site and adjusted to 2007 dollars using the CPI. Time for all other activities (e.g., staff time to conduct a physical exam) and space use estimates for all relevant COMBINE activities were obtained from Project Coordinators at 9 of the 11 COMBINE sites that participated in the cost study. The time spent on COMBINE activities included time spent preparing for each activity. Data on the number of times staff conducted each activity were used to calculate a weighted hourly wage rate. For MM and CBI sessions, labor cost is the product of the actual time spent on each session and the median weighted hourly wage rate across sites for personnel who conducted these sessions. For all other activities, for which time was not tracked in the DMS, the labor cost is the product of the median time across sites spent on the activity and the median hourly wage rate across sites. Space costs equal the median space costs per activity across sites. See Zarkin et al.[13] for more detail on the cost methodology.

To compute laboratory costs, we identified (with the help of the COMBINE Project Coordinators and the cost-effectiveness PIs) key laboratory tests from the COMBINE protocol that are essential if these interventions were implemented in clinical practice. We then associated each test with a CPT procedure code and obtained baseline cost estimates for these procedures from the 2005 Resource Based Relative Values Scale (RBRVS),[14] which is used by Medicare to reimburse for services. These costs were adjusted to 2007 dollars using the CPI.

Effectiveness Measures

The 3 clinical outcomes assessed in our cost-effectiveness analysis are the PDA, the proportion of patients who did not return to heavy drinking days (≥ 5 standard drinks per day for men, ≥ 4 for women), and the proportion of patients who maintained a good clinical outcome[15] (abstinent or moderate drinking without problems; with moderate drinking defined as a maximum of 11 [women] or 14 [men] drinks per week, with no more than 2 days on which more than 3 drinks [women] or 4 drinks [men] were consumed; and problems defined as endorsing 3 or more items on a standardized questionnaire[16] assessing physical, social, and psychological consequences of drinking.); all these outcomes were measured through the end of the 16-week treatment period. These outcomes mirror the primary outcomes from Anton et al.[10] As in the main findings paper,[10] all outcomes were adjusted for baseline PDA and clinical site.

Cost-effectiveness Analysis

All interventions were ranked in increasing order of mean cost (C) for each of the 3 effectiveness measures, regardless of the statistical significance of the cost or effectiveness estimates. Incremental cost-effectiveness ratios ($ICERs_{ij}$), defined as the difference in mean cost divided by the difference in mean effectiveness (E), $(C_j - C_i)/(E_j - E_i)$, where intervention j is the next most costly intervention compared to i, were then computed for each intervention relative to the next most costly option after eliminating treatment options that are economically dominated by other treatments.[17]

An intervention is eliminated through strict dominance if there is another intervention that is less expensive and more effective than the eliminated intervention. An intervention is eliminated through extended dominance if it has a greater ICER than a more costly intervention.[18] In that case, the cost of achieving a given level of the outcome is lower if the dominated intervention is eliminated. The non-dominated interventions that remain comprise the cost-effectiveness frontier (CEF). ICERs are computed and reported for each intervention on the CEF without regard to the statistical significance of the cost or effectiveness differences between interventions.

Interventions that are not on the CEF are not cost-effective alternatives and therefore are excluded from further consideration. Choosing the "optimal" or most cost-effective intervention from among those remaining on the CEF depends on the perspective from which the choice is made. Specifically, economic theory suggests that the optimal intervention is the one with the greatest ICER that is not more than the decision maker's intrinsic valuation or willingness to pay (WTP) for an additional unit of the outcome.[18]

To reflect sampling variability in our cost-effectiveness analysis, we calculated cost-effectiveness acceptability curves (CEACs) as an alternative to confidence intervals for ICERs.[19,20] The CEACs incorporate the inherent variability of the cost and effectiveness estimates (i.e., their statistical significance), and they show the probability that an intervention is the most cost-effective as a function of the policy maker's intrinsic valuation or WTP for the clinical outcome. We used nonparametric bootstrap methods to calculate CEACs for all nine intervention arms (see also UKATT Research Team[11]; Fenwick et al.[20]).

Sensitivity Analysis

In a trial such as COMBINE where medications are a critical component of the intervention, pharmaceutical prices may have a large effect on the cost results. Similarly, as observed in Zarkin et al.,[13] labor costs comprise the largest proportion of activity costs. In our sensitivity analyses, we evaluated cost and cost-effectiveness analyses with alternative pharmaceutical prices and with alternative staff wages. Average Wholesale Price (AWP) was used as the

upper bound for calculating pharmaceutical costs.[21] It has also been used in previous cost and cost-effectiveness studies.[22,23] The AWP published in the Red Book is in most cases the manufacturer's suggested AWP and does not necessarily reflect the actual AWP charged by a wholesaler. The AWP is sometimes referred to as a "sticker price" because it is often higher than the actual price that larger purchasers normally pay. The AWPs for acamprosate and naltrexone are $0.74 per 333 mg tab (versus $0.64 baseline) and $4.29 per 50 mg tab (versus $1.37 baseline), respectively. We varied labor costs by using the 25th and 75th percentiles of sites' labor costs for performing MM and CBI (versus the median baseline). We performed 1-way sensitivity analyses in which we first varied pharmaceutical prices alone (all else the same) and staff wages alone (all else the same as initial values) and then performed 2-way sensitivity analyses in which we varied both pharmaceutical prices and staff wages simultaneously.

RESULTS

Table 1 presents the mean costs of each intervention separated into the following categories: medications, labor costs of MM and CBI, and costs of non-laboratory and laboratory assessments. Non-laboratory assessments included a medical history, a physical exam, and other assessments received by every patient and discussed in Zarkin et al.[13] With the exception of the medication costs, there are no significant differences in cost within a column across the interventions.

The results of the cost-effectiveness analysis for the 3 outcomes are reported in Table 2. Mean (adjusted) cost and effectiveness represent the results per patient in each of the 9 arms in COMBINE. MM + placebo is the least expensive intervention ($409 per patient), and MM + naltrexone + acamprosate + CBI is the most expensive ($1313 per patient). For 2 of the 3 outcomes, CBI only has the smallest mean effectiveness and MM + naltrexone + acamprosate has the largest mean effectiveness for all outcomes.

Mean costs and effectiveness are reported for each outcome followed by the results of the cost-effectiveness analysis. For PDA and the proportion of patients avoiding heavy drinking, CBI only is strictly dominated from an economic perspective by MM + placebo because the latter is less expensive and more effective than the former; for the proportion of patients achieving a good clinical outcome, CBI only is weakly dominated economically. For all outcomes, MM + placebo is not dominated economically (it is the least expensive intervention) and is on the CEF. Moving down the column from MM + placebo to more expensive interventions, MM + naltrexone is less expensive and more effective than all intervening interventions except for MM + naltrexone + acamprosate; thus, these intervening interventions are strictly dominated economically. Moving down the column from MM + naltrexone + acamprosate, the remaining interventions are strictly dominated economically because they are more expensive and less effective than MM + naltrexone + acamprosate.

The cost-effectiveness results based on the means for all 3 outcomes show that only 3 interventions are included in the cost-effective choice set: MM + placebo, MM + naltrexone, and MM + naltrexone + acamprosate (see the shaded interventions in Table 2). The ICER moving from MM + placebo to MM + naltrexone is $42 per percentage point increase in PDA, $2847 per patient of avoiding heavy drinking, and $1690 per patient of achieving a good clinical outcome. The ICER moving from MM + naltrexone to MM + naltrexone + acamprosate is at least 2.5 times greater for all outcomes: $664 per percentage point increase in PDA (more than 15 times greater), $8095 per patient of avoiding heavy drinking, and $7543 per patient of achieving a good clinical outcome.

Figures 1 through 3 present CEACs. These show the probability that each of the interventions is the most cost-effective for alternative values of WTP for the outcomes; WTP represents alternative dollar valuations that may be placed on each outcome by decisions makers (in this case, treatment providers). Because the WTP for each of these outcomes will differ and no definitive values have been established for them in the field, we present alternative WTP values. For PDA (Figure 1), MM + placebo has the highest probability of being the most cost-effective for low WTP values (below $50); for moderate values of WTP ($50 to $350), MM + naltrexone has the highest probability of being the most cost-effective, but that probability decreases as WTP increases and its probability converges to the probability of MM + placebo + CBI. For high values of WTP, MM + naltrexone + acamprosate has the highest probability of being the most cost-effective but its probability never exceeds .4. The other 6 interventions have very small probabilities of being cost-effective.

For the other 2 outcomes (Figures 2 and 3), MM + naltrexone has the highest probability of being the most cost-effective for most of the low values of WTP (below $8000), but for WTP values in excess of $8000, MM + naltrexone + acamprosate has the largest probability of being the most cost-effective (approximately .50). All the other interventions have relatively low probabilities of being optimal (less than .20).

Sensitivity Analysis

The cost-effectiveness results are sensitive to the price of naltrexone, but the results are not sensitive to changes in wages. Under the high pharmaceutical price scenario, naltrexone is approximately 3 times more expensive than the baseline case; acamprosate is approximately 15% more expensive. For all outcomes, MM + naltrexone is no longer a cost-effective intervention at the mean values. For PDA and the proportion of patients with good clinical outcomes, the cost-effective interventions are now MM + placebo, MM + placebo + CBI, and MM + naltrexone + acamprosate; for the proportion of patients not returning to heavy drinking, the cost-effective interventions are now MM + placebo, MM + acamprosate, and MM + naltrexone + acamprosate. ICERs associated with these interventions are similar in magnitude to the baseline values but are uniformly larger in the sensitivity analysis. The results of the 2-way sensitivity analysis are the same as the 1-way analysis when pharmaceutical prices are varied.

COMMENT

This paper presents the first prospective cost and cost-effectiveness study of combining pharmaceutical and behavioral interventions for alcohol dependence. In addition, it is the first cost-effectiveness study for alcohol dependence in the United States to be conducted alongside an RCT (COMBINE). Only 1 previous prospective cost-effectiveness analysis has been published, and it compared social behavior and network therapy to motivational enhancement therapy in the UK.[11]

Our cost and cost-effectiveness analysis is from the perspective of the treatment provider in best clinical practice rather than from the COMBINE research protocol perspective. This perspective allows policy makers to apply the results in a real-world clinical setting. Previous cost-effectiveness literature of pharmaceutical interventions for alcohol dependence is limited and mainly represents the results of statistical models. No previous prospective studies exist on the cost and cost-effectiveness of treatment for alcohol dependence with naltrexone, and many acamprosate studies are based on statistical models (e.g., Poldrugo et al.[24]; Palmer et al.[25]) or represent the health care system perspective (e.g., Schadlich and Brecht[26]). Rychlik et al.[27] is a prospective cohort study of the cost-effectiveness of acamprosate therapy.

The cost-effectiveness analysis based on the means of cost and effectiveness yields 3 cost-effective options: MM + placebo, MM + naltrexone, and MM + naltrexone + acamprosate. Because MM + placebo is the least costly intervention and MM + naltrexone + acamprosate has the largest mean effectiveness for all 3 outcomes, these interventions are included in the cost-effective choice set. Based on mean effectiveness alone for PDA, MM + naltrexone and MM + placebo + CBI are very similar and might be viewed as equivalent in a cost-effectiveness analysis, but the costs of MM + naltrexone are less making it more attractive on cost-effectiveness grounds. Clinically, MM + placebo may not be a feasible treatment option because physicians do not prescribe placebos, which leaves MM + naltrexone and MM + naltrexone + acamprosate as the 2 viable cost-effective options for all three outcomes.

The statistical tests in Anton et al.[10] were the clinical study's prespecified tests of main effects and interactions. These did not find a clinical benefit for acamprosate either as a main effect or in 2- or 3-way interactions; pairwise comparisons, such as between MM + naltrexone and MM + naltrexone + acamprosate, were not primary or secondary hypotheses. In contrast, the prespecified comparisons for the cost-effectiveness analyses involved looking at each treatment intervention relative to every other intervention in terms of the joint distribution of costs and effectiveness. Further, the pairwise comparisons presented here are not formal statistical tests of efficacy; on efficacy alone, MM + naltrexone + acamprosate is not significantly better than MM + naltrexone.[10] However, based on the joint distribution of cost and effectiveness, MM + naltrexone + acamprosate may be a cost-effective choice that is selected by decision makers under certain circumstances.

The choice of MM + naltrexone + acamprosate over MM + naltrexone depends on whether the cost of the incremental increase in mean effectiveness is worth it to the decision maker. For PDA, MM + naltrexone + acamprosate has only a slightly larger mean effectiveness than MM + naltrexone (0.5 PDA) but has approximately 50% larger mean cost per patient. This translates into an ICER for an additional percentage point increase in PDA of $664, which is an order of magnitude greater than going from MM+ placebo to MM + naltrexone. If decision makers place a value on increases in PDA equal to or in excess of $664, they would be willing to pay the incremental cost for MM + naltrexone + acamprosate; otherwise, they will choose MM + naltrexone. For the proportion of patients who avoid heavy drinking and the proportion of patients who achieve a good clinical outcome, the ICERs for MM + naltrexone + acamprosate relative to MM + naltrexone is approximately 3 to 4 times larger (approximately $7500 to $8000 per patient) compared to going from MM + placebo to MM + naltrexone. If decision makers value increases in mean effectiveness more than the incremental costs of achieving them, they will choose the interventions with the greater mean cost and effectiveness.

The CEAC analysis shows that for all three outcomes, the probabilities that any of the interventions are the most cost-effective are relatively small, except at the very lowest WTP values. Beyond a WTP of $350 per percentage point increase in PDA, MM + naltrexone + acamprosate has the largest probability of being the most cost-effective intervention, although with a relatively small probability of between 0.3 and 0.4. For decision makers with a relatively high dollar value for PDA who choose MM + naltrexone + acamprosate because it has the highest probability of being cost-effective, this choice will turn out not to be the most cost-effective choice 60% to 70% of the time. Similarly, for the proportion of patients avoiding heavy drinking and the proportion of patients achieving good clinical outcomes, the probability of MM + naltrexone + acamprosate being the most cost-effective for large values of WTP is also relatively small, in the range of 0.5 to 0.6

The low probabilities of being cost-effective even at high values of WTP are caused by 2 key factors: the large number of treatment alternatives (9 versus the usual 2 or 3 alternatives in most CEA studies), which lowers the probability of choosing any one alternative, all else equal; and the similarity of many of the mean effectiveness estimates making it difficult to distinguish between different interventions.

The results are sensitive to the price of naltrexone, which is not unexpected given that the sensitivity analysis assumed the sticker prices for naltrexone and acamprosate, which increases the naltrexone price by over 200% (or over 3X) but only increases the price of acamprosate by 15%. We believe that most providers (and almost certainly large providers) will have access to naltrexone at the discounted baseline values, but, to the extent that they do not, our sensitivity results may provide a more accurate perspective of the cost-effectiveness of the COMBINE intervention.

Our study has 3 primary limitations. First, our cost analysis relies on the judgment of the cost-effectiveness study PIs as to which activities are primarily research-related and which would be used in best clinical practice.[13] To minimize this issue, we implemented a consensus approach to achieve agreement on best clinical practice activities. Importantly, each intervention arm incurs almost the exact same cost for these activities (the exception is CBI), so any errors in this task will have no differential impact across the arms and will not affect the cost-effectiveness analysis. Second, although we have attempted to identify activities that would be part of best clinical practice for the treatment provider perspective, the treatment regimen we use in our costing algorithm follows the COMBINE protocol. We expect that patients are seen more frequently in a clinical trial compared to best clinical practice so we expect our cost estimates to be upper bounds of the actual best practice treatment costs. Future work may want to look at the cost and cost-effectiveness from other perspectives, such as the third-party payer or the patient. Third, our cost-effectiveness results depend on the interventions that were included in the COMBINE study. An alternative set of interventions provides different comparisons between cost and effectiveness, and different cost-effectiveness results. Furthermore, the cost-effectiveness results may differ if alternative clinical and economic endpoints were used (e.g., quality of life, overall functioning).

In spite of these limitations, our cost study provides an important analysis of the cost and cost-effectiveness of the COMBINE therapies. As is typical in cost-effectiveness studies, the choice of the optimal (i.e., most cost-effective) intervention depends on the value placed on the outcomes by the ultimate decision maker. Furthermore, decision makers may have different preferences for the 3 outcomes, and their choice of the optimal intervention may differ by clinical outcome. The similarity of many of the mean effectiveness estimates suggests that future work that explores moderators of treatment outcome has the potential to improve the understanding of both treatment outcome and its cost-effectiveness.

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COMBINE Cost-Effectiveness Project Coordinators and others involved in cost-effectiveness study

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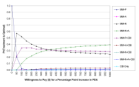

Figure 1.
Cost-Effectiveness Acceptability Curve—Percent Days Abstinent

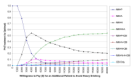

Figure 2.
Cost-Effectiveness Acceptability Curve—Proportion of Patients Who Avoid Heavy Drinking

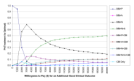

Figure 3.
Cost-Effectiveness Acceptability Curve—Proportion of Patients with Good Clinical Outcomes

Table 1

Costs of Treatment Conditions (in 2007 dollars)

			Mean Cost of Labor		Mean Cost of Assessments		
Treatment Arm	**N**	**Mean Cost of Meds**	**MM**	**CBI**	**Non-Lab**	**Lab**	**Mean Total Cost of Treatment**
MM + placebo	153	---------	$167.38	---------	$132.29	$109.58	$409.25
CBI only	157	---------	---------	$338.26	$109.44	$104.89	$552.59
MM + naltrexone	154	$268.45	$162.63	---------	$131.22	$108.86	$671.16
MM + acamprosate	152	$346.14	$163.14	---------	$131.28	$107.19	$747.85
MM + placebo + CBI	156	---------	$164.62	$349.63	$132.98	$110.67	$757.90
MM + naltrexone + acamprosate	148	$604.93	$159.28	---------	$131.01	$107.83	$1003.06
MM + naltrexone + CBI	155	$287.22	$163.88	$342.46	$132.89	$110.08	$1036.53
MM + acamprosate + CBI	151	$388.08	$162.72	$331.85	$132.85	$110.37	$1125.86
MM + naltrexone + acamprosate + CBI	157	$601.07	$154.25	$318.06	$131.32	$108.25	$1312.96
All treatments	1383	$415.46	$162.23	$336.05	$129.43	$108.63	$845.91

Abbreviations: CE, cost-effectiveness; MM, medical management; CBI, combined behavioral intervention.

Table 2

Cost-Effectiveness Analysis

		Percent Days Abstinent		Proportion of Patients that Avoid Heavy Drinking		Proportion of Patients with Good Clinical Outcomes	
		(1)	(2)	(3)	(4)	(5)	(6)
Treatment Arm	**Mean Cost**	**Mean Effectiveness**	**Incremental CE Ratio (ΔC/ΔE, $)**	**Mean Effectiveness**	**Incremental CE Ratio (ΔC/ΔE, $)**	**Mean Effectiveness**	**Incremental CE Ratio (ΔC/ΔE, $)**
MM + placebo	**409.25 (6.49)**	**73.8 (2.318)**	**—**	**0.257 (0.034)**	—	**0.583 (0.044)**	—
CBI only	552.59 (15.59)	66.7 (2.545)	Economically Dominated	0.241 (0.037)	Dominated	0.608 (0.042)	Economically Dominated*
MM + naltrexone	**671.16 (16.80)**	**80.0 (2.013)**	**42.24**	**0.349 (0.036)**	**2,846.85**	**0.738 (0.043)**	**1,689.74**
MM + acamprosate	746.85 (19.37)	75.6 (2.202)	Economically Dominated	0.326 (0.035)	Dominated	0.608 (0.042)	Economically Dominated
MM + placebo + CBI	757.90 (16.90)	79.8 (2.033)	Economically Dominated	0.305 (0.037)	Dominated	0.714 (0.039)	Economically Dominated
MM + naltrexone + acamprosate	**1003.06 (31.71)**	**80.5 (1.898)**	**663.80**	**0.390 (0.036)**	**8,095.12**	**0.782 (0.037)**	**7,543.18**
MM + naltrexone + CBI	1036.53 (23.56)	75.9 (2.376)	Economically Dominated	0.343 (0.038)	Dominated	0.745 (0.036)	Economically Dominated
MM + acamprosate + CBI	1125.87 (28.78)	78.3 (2.053)	Economically Dominated	0.351 (0.035)	Dominated	0.745 (0.038)	Economically Dominated
MM + naltrexone + acamprosate + CBI	1312.96 (40.43)	77.6 (2.257)	Economically Dominated	0.278 (0.036)	Dominated	0.740 (0.038)	Economically Dominated

Abbreviations: CE, cost-effectiveness; MM, medical management; CBI, combined behavioral intervention.

*Weakly dominated by naltrexone.

Means are predicted outcomes from COMBINE sample. Standard errors from bootstrapped samples are in parentheses. Ordered by ascending mean cost of treatment.