Cost and Cost-effectiveness of the COMBINE Study in Alcohol-Dependent Patients

By: Gary A. Zarkin, Jeremy W. Bray, Arnie Aldridge, Debanjali Mitra, Michael Mills, David J. Couper, Ron A. Cisler

Made available courtesy of American Medical Association
http://dx.doi.org/doi:10.1001/archpsyc.65.10.1214

Abstract:

The COMBINE (Combined Pharmacotherapies and Behavioral Intervention) 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.

Keywords: COMBINE | cost | cost-effectiveness | alcoholism | alcohol dependence treatment

***Note: Full text of article below

Cost and Cost-effectiveness of the COMBINE Study in Alcohol-Dependent Patients

Gary A. Zarkin, PhD; Jeremy W. Bray, PhD; Arnie Aldridge, MS; Debanjali Mitra, MA; Michael J. Mills, MA; David J. Couper, PhD; Ron A. Cisler, PhD; for the COMBINE Cost-Effectiveness Research Group

Context: The COMBINE (Combined Pharmacotherapies and Behavioral Intervention) 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 Study interventions after 16 weeks of treatment.

Design: A prospective cost and cost-effectiveness study of a randomized controlled clinical trial.

Setting: Eleven US clinical sites.

Participants: One thousand three hundred eighty-three patients having a diagnosis of primary alcohol dependence.

Interventions: The study included 9 treatment groups; 4 groups received medical management for 16 weeks with naltrexone, 100 mg/d, acamprosate, 3 g/d, or both, and/or placebo; 4 groups received the same therapy as mentioned earlier with combined behavioral intervention; and 1 group received combined behavioral intervention only.

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

Results: On the basis of the mean values of cost and effectiveness, 3 interventions are cost-effective options relative to the other interventions for all 3 outcomes: medical management (MM) with placebo ($409 per patient), MM plus naltrexone therapy ($671 per patient), and MM plus combined naltrexone and acamprosate therapy ($1003 per patient).

Conclusions: To our knowledge, this is only the second prospective cost-effectiveness study with a randomized controlled clinical trial design that has been performed for the treatment of alcohol dependence. Focusing only on effectiveness, MM-naltrexone-acamprosate therapy is not significantly better than MM-naltrexone therapy. However, considering cost and cost-effectiveness, MM-naltrexone-acamprosate therapy may be a better choice, depending on whether the cost of the incremental increase in effectiveness is justified by the decision maker.

Trial Registration: clinicaltrials.gov Identifier: NCT00006206

Arch Gen Psychiatry. 2008;65(10):1214-1221

Author Affiliations: RTI International, Research Triangle Park (Drs Zarkin and Bray, Messrs Aldridge and Mills, and Ms Mitra), and University of North Carolina at Chapel Hill (Dr Couper), North Carolina; and Center for Urban Population Health, University of Wisconsin–Milwaukee, University of Wisconsin School of Medicine and Public Health, and Aurora Health Care, Inc (Dr Cisler), Milwaukee, Wisconsin.
Group Information: A list of the current members of the COMBINE Cost-effectiveness Research Group is given at the end of this article.

ALCOHOL USE IS THE THIRD leading preventable cause of death,[1] and alcohol abuse and dependence impose substantial costs on society. In 1998, the estimated societal cost of alcohol abuse in the United States was $184 billion.[2] The sizable economic and societal 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[3] and 2 pharmacotherapies—naltrexone and acamprosate[4,5]—have been shown to be efficacious.

Based on evidence for both approaches, the COMBINE (Combined Pharmacotherapies and Behavioral Interventions) Study was designed to examine the effects of combining behavioral therapy and pharmacotherapy in the treatment of alcohol dependence.[6-9] COMBINE, a multicenter, randomized, controlled clinical trial sponsored by the National Institute on Alcohol Abuse and Alcoholism, 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 re-

ceived MM and were randomized to receive acamprosate or matching placebo plus naltrexone or matching placebo plus either CBI or no additional behavioral therapy. The ninth treatment group received CBI only (no MM or medication). The prespecified primary analyses involved analysis of variance–type tests of main effects and interactions in the $2 \times 2 \times 2$ factorial part of the study. Pairwise comparisons between treatment groups were not prespecified analyses and were not reported in the main findings article by Anton et al.[10]

Results for the primary clinical outcomes from the COMBINE Study are available in Anton et al.[10] In brief, in the 16-week treatment period, patients receiving MM-naltrexone therapy, CBI, or both had better drinking outcomes than those receiving MM alone. The combination of naltrexone-CBI therapy showed no incremental benefit over CBI or naltrexone therapy alone. Acamprosate therapy 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 enable efficient allocation of these resources. In this article, we evaluate the cost and cost-effectiveness of the COMBINE Study after 16 weeks of treatment. The only other randomized, controlled, clinical trial–designed cost-effectiveness study[11] did not evaluate combinations of pharmaceutical and behavioral interventions, as in our study.

<div style="text-align:center">

METHODS

</div>

RECRUITMENT AND RANDOMIZATION

Participants were recruited via 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 the National Institute on Alcohol Abuse and Alcoholism. Eligibility criteria included the following: (1) alcohol dependence as determined by *DSM-IV*[12] criteria; (2) 4 to 21 days of abstinence; and (3) more than 14 drinks per week for women or 21 drinks per week for men, 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 before baseline evaluation. Exclusion criteria included the following: (1) history of other substance abuse excluding nicotine or cannabis according to *DSM-IV* criteria in the last 90 days (6 months for opiate abuse) or at urine drug screening, (2) psychiatric disorder requiring medication, or (3) unstable medical condition (eg, 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. Racial/ethnic minorities made up 23% of the sample. In the 30 days before randomization, 2.3% of patients underwent medical detoxification and 7.7% received inpatient treatment. At baseline, mean percentage of days abstinent (PDA) was 25.0% and mean number of drinks per drinking day was 12.5.

COST ESTIMATION

We used a microcosting approach to compute the costs of COMBINE Study therapies from the perspective of the treatment provider[13] because this perspective is most relevant to decision makers in best clinical practice. As described in Zarkin et al,[13] we identified COMBINE Study 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 estimated the cost of each of these activities, updating unit cost estimates to 2007 US dollars.

The cost of each COMBINE Study intervention was determined as the sum of space, labor, medication, and laboratory costs for each treatment condition. We obtained pharmaceutical costs for acamprosate and naltrexone from the Federal Supply Schedule, in which prices are negotiated by the Veterans Administration and are publicly available. They are based on the prices that manufacturers charge their most-favored nonfederal customers. The Federal Supply Schedule price of acamprosate is $0.64 per 333-mg tablet, and of naltrexone is $1.37 per 50-mg tablet. This translates to a daily cost 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 data management system. These data were collected prospectively as part of the COMBINE Study. Salary data, including fringe benefits, for all staff involved in COMBINE Study interventions were obtained from the cost-effectiveness principal investigators at each site and adjusted to 2007 US dollars using the Consumer Price Index. Time for all other activities (eg, staff time to conduct a physical examination) and space use estimates for all relevant COMBINE Study activities were obtained from project coordinators at 9 of the 11 COMBINE Study sites that participated in the cost study. The time spent on COMBINE Study 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. For MM and CBI sessions, labor cost is the product of the time spent on each session and the median weighted hourly wage across sites for personnel who conducted these sessions. For all other activities, for which time was not tracked in the data management system, the labor cost is the product of the median time across sites spent on the activity and the median hourly wage across sites. Space costs equal the median space costs per activity across sites. See Zarkin et al[13] for more details of the cost methods.

To compute laboratory costs, we identified (with the help of the COMBINE Study project coordinators and the cost-effectiveness principal investigators) key laboratory tests from the COMBINE Study protocol that are essential if these interventions are implemented in clinical practice. We then associated each test with a *Current Procedural Terminology* procedure code and obtained baseline cost estimates for these procedures from the 2005 Resource-Based Relative Value Scale,[14] which is used by Medicare to reimburse for services. These costs were adjusted to 2007 US dollars using the Consumer Price Index.

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 and ≥4 drinks per day 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 drinks per week for women or 14 drinks per week for men, with no more than 2 days on which women consumed more than 3 drinks or men consumed 4 drinks; and problems defined as endorsing 3 items or more on a standardized questionnaire[16] that assessed social, physical, and psychological consequences of drinking). All of

Table 1. Cost of Treatments

Treatment	No. of Patients	Mean Cost, $					
		Medication[a]	Labor[a]		Assessments[a]		Total Cost of Treatment
			MM	CBI	Nonlaboratory	Laboratory	
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[b]	**1383**	415.46	162.23	336.05	129.43	108.63	**845.91**

Abbreviations: CBI, combined behavioral intervention; MM, medical management.
[a] Data do not sum to total cost of treatment due to rounding.
[b] The mean costs of medication, labor for MM, and labor for CBI are conditional on treatment arms that provided the relevant service; therefore, the sum of these means will not equal the mean total cost of treatment across all treatments.

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 that article,[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 C 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 with intervention 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 nondominated interventions that remain make up the cost-effectiveness frontier. The ICERs are computed and reported for each intervention on the cost-effectiveness frontier without regard to the statistical significance of the cost or effectiveness differences between interventions.

Interventions that are not on the cost-effectiveness frontier 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 cost-effectiveness frontier 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 as an alternative to confidence intervals for ICERs.[19,20] The cost-effectiveness acceptability curves incorporate the inherent variability of the cost and effectiveness estimates (ie, 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 cost-effectiveness acceptability curves for all 9 intervention arms (see also UKATT Research Team[11] and Fenwick et al[20]).

SENSITIVITY ANALYSIS

In a trial such as the COMBINE Study in which medications are a critical component of the intervention, pharmaceutical prices may have a large effect on the cost results. Similarly, as observed by Zarkin et al,[13] labor costs make up the largest percentage 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 was used as the upper limit for calculating pharmaceutical costs[21] and has also been used in previous cost and cost-effectiveness studies.[22,23] The average wholesale price published in the *Red Book* is in most cases the manufacturer's suggested average wholesale price and does not necessarily reflect the actual average wholesale price charged by a wholesaler. The average wholesale price is sometimes referred to as the "sticker price" because it is often higher than the price that large purchasers normally pay. The average wholesale prices for acamprosate and naltrexone are $0.74 per 333-mg tablet (vs $0.64 baseline) and $4.29 per 50-mg tablet (vs $1.37 baseline), respectively. We varied labor costs by using the 25th and 75th percentiles of site labor costs for performing MM and CBI (vs 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 gives the mean costs of each intervention separated into the following categories: medications, labor costs of MM and CBI, and costs of laboratory and nonlaboratory assessments. Nonlaboratory assessments included a medical history, a physical examination, and other assessments received by every patient and discussed in Zarkin et al.[13] With the exception of medication costs, there are no significant differences in cost within a column across the interventions.

Table 2. Cost-effectiveness Analysis[a]

Treatment	Mean Cost	Percent Days Abstinent		Proportion of Patients Who Avoid Heavy Drinking		Proportion of Patients With Good Clinical Outcomes	
		Mean Effectiveness	ICER ($\Delta C/\Delta E$, $)	Mean Effectiveness	ICER ($\Delta C/\Delta E$, $)	Mean Effectiveness	ICER ($\Delta C/\Delta E$, $)
MM-placebo[b]	**409.25 (6.49)**	**73.80 (2.32)**		**0.26 (0.03)**		**0.58 (0.04)**	
CBI only	552.59 (15.59)	66.70 (2.55)	Economically dominated	0.24 (0.04)	Economically dominated	0.61 (0.04)	Economically dominated[c]
MM-naltrexone	**671.16 (16.80)**	**80.00 (2.01)**	**42.24**	**0.35 (0.04)**	**2846.85**	**0.74 (0.04)**	**1689.74**
MM-acamprosate	746.85 (19.37)	75.60 (2.20)	Economically dominated	0.33 (0.04)	Economically dominated	0.61 (0.04)	Economically dominated
MM-placebo-CBI	757.90 (16.90)	79.80 (2.03)	Economically dominated	0.31 (0.04)	Economically dominated	0.71 (0.04)	Economically dominated
MM-naltrexone-acamprosate	**1003.06 (31.71)**	**80.50 (1.90)**	**663.80**	**0.39 (0.04)**	**8095.12**	**0.78 (0.04)**	**7543.18**
MM-naltrexone-CBI	1036.53 (23.56)	75.90 (2.38)	Economically dominated	0.34 (0.04)	Economically dominated	0.75 (0.04)	Economically dominated
MM-acamprosate-CBI	1125.87 (28.78)	78.30 (2.05)	Economically dominated	0.35 (0.04)	Economically dominated	0.75 (0.04)	Economically dominated
MM-naltrexone-acamprosate-CBI	1312.96 (40.43)	77.60 (2.26)	Economically dominated	0.28 (0.04)	Economically dominated	0.74 (0.04)	Economically dominated

Abbreviations: CBI, combined behavioral intervention; $\Delta C/\Delta E$, change in cost over change in effectiveness; ICER, incremental cost-effectiveness ratio; MM, medical management.
[a] Means are predicted outcomes from COMBINE sample; standard errors from bootstrapped samples are in parentheses. Ordered by ascending mean cost of treatment.
[b] Interventions in boldface are included in the cost-effective choice set based on mean values of cost and effectiveness.
[c] Weakly dominated by MM-naltrexone.

The results of the cost-effectiveness analysis for the 3 outcomes are given in **Table 2**. Mean (adjusted) cost and effectiveness represent the results per patient in each of the 9 arms of the COMBINE Study. The least expensive intervention ($409 per patient) was MM-placebo, and the most expensive ($1313 per patient) was MM-naltrexone-acamprosate-CBI. For 2 of the 3 outcomes, CBI-only demonstrated the smallest mean effectiveness, and MM-naltrexone-acamprosate demonstrated the largest mean effectiveness for all outcomes.
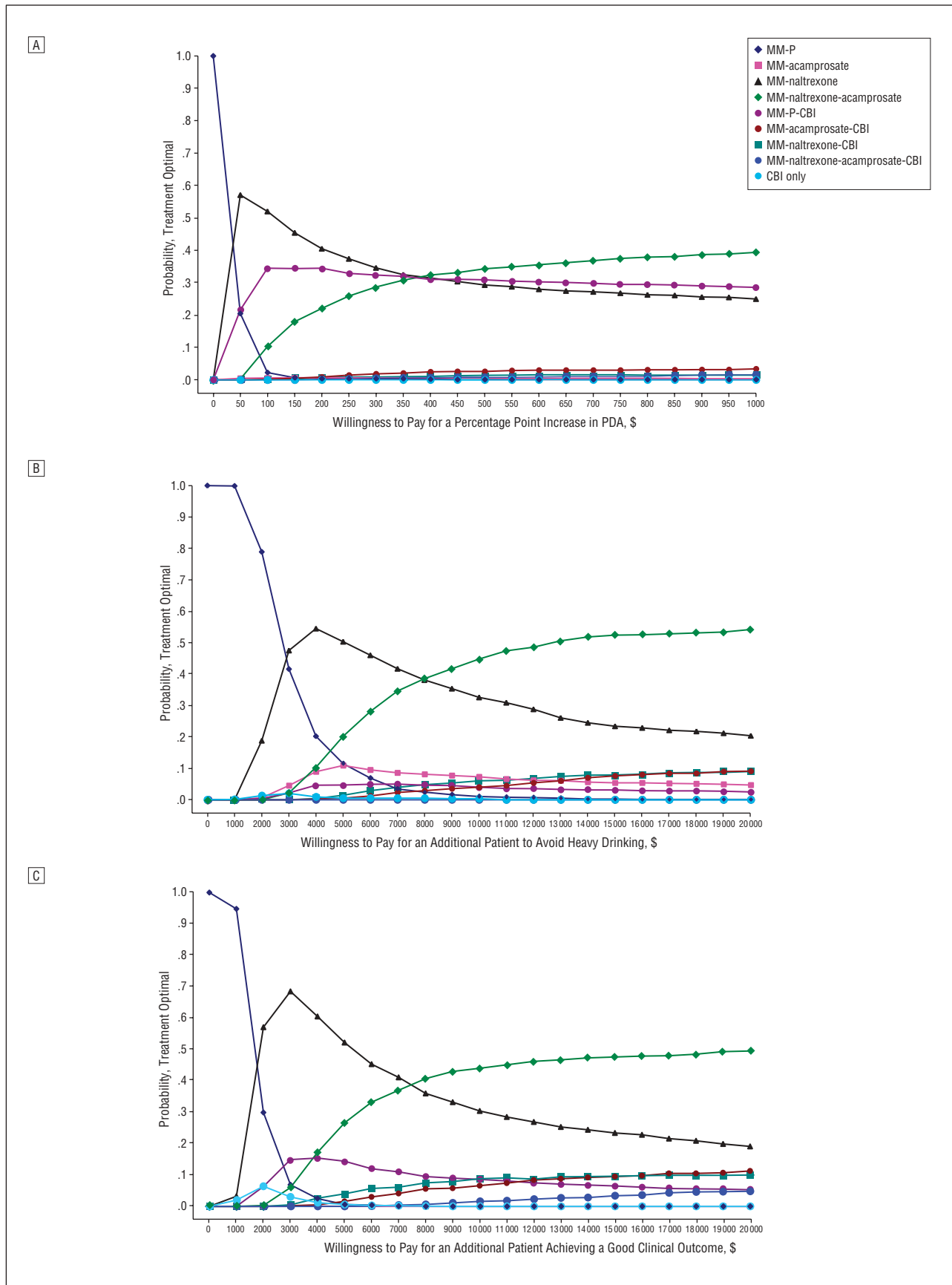
Mean costs and effectiveness are reported for each outcome, followed by the results of the cost-effectiveness analysis. For PDA and the proportion of patients avoiding heavy drinking, CBI-only is strictly dominated from an economic perspective by MM-placebo because MM-placebo therapy is less expensive and more effective than CBI; for the proportion of patients achieving a good clinical outcome, CBI-only is weakly economically dominated. For all outcomes, MM-placebo is not economically dominated (it is the least expensive intervention) and is on the cost-effectiveness frontier. 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 economically dominated. Moving down the column from MM-naltrexone-acamprosate, the remaining interventions are strictly economically dominated 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 boldface 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 2½ 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.

The **Figure** shows cost-effectiveness acceptability curves, which show the probability that each of the interventions is the most cost-effective for alternative values of WTP for the outcomes. The WTP represents alternative dollar valuations that may be placed on each outcome by decision 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, A), MM-placebo has the highest probability of being the most cost-effective for low WTP values (<$50); for moderate values of WTP ($50-$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; however, its probability never exceeds .40. The other 6 interventions have small probabilities of being cost-effective.

For the other 2 outcomes (Figure, B and Figure, C), MM-naltrexone has the highest probability of being the most cost-effective for most of the low values of WTP (<$8000); however, for WTP values greater than $8000, MM-naltrexone-acamprosate has the largest probability of being the most cost-effective (approximately .50). All of the other interventions have relatively low probabilities of being optimal (<.20).

Figure. Cost-effectiveness acceptability curves. A, Percentage of days abstinent (PDA). B, Cost-effectiveness acceptability curve: Proportion of patients who avoid heavy drinking. C, Cost-effectiveness acceptability curve: Proportion of patients with good clinical outcomes. CBI indicates combined behavioral intervention; MM medical management; and P, placebo.

SENSITIVITY ANALYSIS

The cost-effectiveness results are sensitive to the price of naltrexone; however, 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. The 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

To our knowledge, ours is 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 a randomized, controlled, clinical trial (ie, COMBINE Study). Only 1 previous prospective cost-effectiveness analysis has been published, and it compared social behavior and network therapy to motivational enhancement therapy in the United Kingdom.[11]

Our cost and cost-effectiveness analysis is from the perspective of the treatment provider in best clinical practice rather than from the perspective of the COMBINE Study research protocol. This perspective enables 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 primarily represents the results of statistical models. No previous prospective studies exist of the cost and cost-effectiveness of treatment for alcohol dependence with naltrexone, and many acamprosate studies are based on statistical models (eg, Poldrugo et al[24] and Palmer et al[25]) or represent the health care system perspective (eg, Schädlich and Brecht[26]). Rychlik et al[27] conducted 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. On the basis of mean effectiveness alone for PDA, MM-naltrexone and MM-placebo-CBI are similar and might be viewed as equivalent in a cost-effectiveness analysis; however, MM-naltrexone is less costly, which makes it

more attractive on cost-effectiveness grounds. Clinically, MM-placebo may not be a feasible treatment option because physicians do not prescribe placebos; thus, MM-naltrexone and MM-naltrexone-acamprosate are the 2 viable cost-effective options for all 3 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 therapy either as a main effect or in 2- or 3-way interactions; pairwise comparisons between MM-naltrexone and MM-naltrexone-acamprosate were not primary or secondary hypotheses. In contrast, the prespecified comparisons for the cost-effectiveness analyses involved investigating each treatment intervention relative to every other intervention in terms of the joint distribution of costs and effectiveness. Further, the pairwise comparisons presented herein are not formal statistical tests of efficacy; on efficacy alone, MM-naltrexone-acamprosate is not significantly better than MM-naltrexone.[10] However, on the basis of 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 justifiable by the decision maker. For PDA, MM-naltrexone-acamprosate has only a slightly larger mean effectiveness than MM-naltrexone (0.5 PDA) but has an 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 switching from MM-placebo to MM-naltrexone. If decision makers place a value on increases in PDA equal to or greater than $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 ICER for MM-naltrexone-acamprosate relative to MM-naltrexone is approximately 3 to 4 times larger (approximately $7500 to $8000 per patient) compared with switching 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 cost-effectiveness acceptability curve analysis shows that for all 3 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 .30 and .40. 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 not be the most cost-effective choice 60% to 70% of the time. Similarly, for the proportion of patients who avoid heavy drinking and the proportion of patients who achieve a good clinical out-

come, the probability of MM-naltrexone-acamprosate being the most cost-effective for large values of WTP is also relatively small, in the range of .50 to .60.

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 vs the usual 2 or 3 alternatives in most cost-effective analysis studies), which lowers the probability of choosing any one alternative, all else being equal; and the similarity of many of the mean effectiveness estimates, which makes it difficult to differentiate between the various interventions.

The results are sensitive to the price of naltrexone, which is expected because the sensitivity analysis assumed the sticker prices for naltrexone and acamprosate, which increases the naltrexone price by more than 200% (or >3-fold) 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; however, to the extent that they do not, our sensitivity results may provide a more accurate perspective of the cost-effectiveness of the COMBINE Study intervention.

Our study has 3 primary limitations. First, our cost analysis relies on the judgment of the cost-effectiveness study principal investigators 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. Each intervention arm except CBI incurs almost the exact same cost for these activities; therefore, any errors in this task will have no differential effect 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 from the perspective of the treatment provider, the treatment regimen we use in our costing algorithm follows the COMBINE Study protocol. We expect that patients are seen more frequently in a clinical trial compared with best clinical practice; thus, we expect our cost estimates to be the upper limits of the actual best practice treatment costs. Future work may examine 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 end points are used (eg, quality of life and overall functioning).

Despite these limitations, our cost study provides an important analysis of the cost and cost-effectiveness of the COMBINE Study therapies. As is typical in cost-effectiveness studies, the choice of the optimal (ie, 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.

REFERENCES

1. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000 [published corrections appear in *JAMA*. 2005;293(3):293-294 and 298]. *JAMA*. 2004;291(10):1238-1245.
2. Harwood H. Updating estimates of the economic costs of alcohol abuse in the

United States: estimates, update methods, and data. Reported in: Harwood H, Fountain D, Livermore G. *The Economic Costs of Alcohol and Drug Abuse in the United States 1992*. Rockville, MD: National Institutes of Health; 1998. NIH publication No. 98-4327.

3. Longabaugh R, Zweben A, LoCastro JS, Miller WR. Origins, issues and options in the development of the combined behavioral intervention. *J Stud Alcohol Suppl*. July 2005;(15):179-187.

4. Litten RZ, Allen JP. Advances in the development of medications for alcoholism treatment. *Psychopharmacology (Berl)*. 1998;139(1-2):20-33.

5. Mason BJ, Ownby RL. Acamprosate for the treatment of alcohol dependence: a review of double-blind, placebo-controlled trials. *CNS Spectr*. 2000;5(2):58-69.

6. The COMBINE Study Research Group. Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: rationale and methods. *Alcohol Clin Exp Res*. 2003;27(7):1107-1122.

7. Mattson ME, Litten RZ. Combining treatments for alcoholism: why and how? *J Stud Alcohol Suppl*. July 2005;(15):6-16.

8. Pettinati HM, Weiss RD, Dundon W, et al. A structured approach to medical management: a psychosocial intervention to support pharmacotherapy in the treatment of alcohol dependence. *J Stud Alcohol Suppl*. July 2005;(15):168-178.

9. Swift R, Pettinat HM. Choosing pharmacotherapies for the COMBINE Study: process and procedures; an investigational approach to combination pharmacotherapy for the treatment of alcohol dependence. *J Stud Alcohol Suppl*. July 2005; (15):140-147.

10. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A; COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE Study; a randomized controlled trial. *JAMA*. 2006;295(17):2003-2017.

11. UKATT Research Team. Cost effectiveness of treatment for alcohol problems: findings of the randomised UK alcohol treatment trial (UKATT). *BMJ*. 2005; 331(7516):544-548.

12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.

13. Zarkin GA, Bray JW, Mitra D, Cisler RA, Kivlahan DR. Cost methodology of COMBINE. *J Stud Alcohol Suppl*. July 2005;(15):50-55.

14. Ingenix, Inc. *The Essential RBRVS: A Comprehensive Listing of RBRVS Values for CPT and HCPCS Codes*. Salt Lake City, UT: Ingenix Inc; 2005.

15. Cisler RA, Zweben A. Development of a composite measure for assessing alcohol treatment outcome. *Alcohol Clin Exp Res*. 1999;23(2):263-271.

16. Miller WR, Tonigan JS, Longabaugh R. *The Drinker Inventory of Consequences (DrInC): An Instrument for Assessing Adverse Consequences of Alcohol Abuse*. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism; 1995.

17. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR; Panel on Cost-effectiveness in Health and Medicine. Guidelines for pharmacoeconomic studies: recommendations from the Panel on Cost-effectiveness in Health and Medicine. *Pharmacoeconomics*. 1997;11(2):159-168.

18. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. New York, NY: Oxford University Press; 2005.

19. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ*. 2001;10(8):779-787.

20. Fenwick E, Marshall DA, Levy AR, Nichol G. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. *BMC Health Serv Res*. 2006;6(1):52-59.

21. Thomson MicroMedex. *RedBook for Windows*. Version 61127, Vol 41. Montvale, NJ: Thomson PDR; July 2006.

22. Mobley LR, Hoerger TJ, Wittenborn JS, Galuska DA, Rao JK. Cost-effectiveness of osteoporosis screening and treatment with hormone replacement therapy, raloxifene, or alendronate. *Med Decis Making*. 2006;26(2):194-206.

23. DiSantostefano RL, Biddle AK, Lavelle JP. The long-term cost effectiveness of treatments for benign prostatic hyperplasia. *Pharmacoeconomics*. 2006;24 (2):171-191.

24. Poldrugo F, Haeger DA, Comte S, Walburg J, Palmer AJ. A critical review of pharmacoeconomic studies of acamprosate. *Alcohol Alcohol*. 2005;40(5):422-430.

25. Palmer AJ, Neeser K, Weiss C, Brendt A, Comte S, Fox M. The long-term cost-effectiveness of improving alcohol abstinence with adjuvant acamprosate. *Alcohol Alcohol*. 2000;35(5):478-492.

26. Schädlich PK, Brecht JG. The cost effectiveness of acamprosate in the treatment of alcoholism in Germany: economic evaluation of the Prevention of Relapse with Acamprosate in the Management of Alcoholism (PRAMA) Study. *Pharmacoeconomics*. 1998;13(6):719-730.

27. Rychlik R, Siedentop H, Pfeil T, Daniel D. Cost-effectiveness of adjuvant treatment with acamprosate in maintaining abstinence in alcohol dependent patients. *Eur Addict Res*. 2003;9(2):59-64.