

# Revisiting the Cost-Effectiveness of the COMBINE Study for Alcohol Dependent Patients

## *The Patient Perspective*

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**Objective:** Most cost and cost-effectiveness studies of substance abuse treatments focus on the costs to the provider/payer. Although this perspective is important, the costs incurred by patients should also be considered when evaluating treatment. This article presents estimates of patients' costs associated with the Combined Pharmacotherapies and Behavioral Interventions (COMBINE) alcohol treatments and evaluates the treatments' cost-effectiveness from the patient perspective.

**Study Design:** A prospective cost-effectiveness study of patients in COMBINE, a randomized controlled clinical trial of 9 alternative alcohol treatment regimens involving 1383 patients with diagnoses of primary alcohol dependence across 11 US clinic sites. We followed a microcosting approach that allowed estimation of patients' costs for specific COMBINE treatment activities. The primary clinical outcomes from COMBINE are used as indicators of treatment effectiveness.

**Results:** The average total patient time devoted to treatment ranged from about 30 hours to 46 hours. Time spent traveling to and from treatment sessions and participation in self-help meetings accounted for the largest portion of patient time costs. The cost-effectiveness results indicate that 6 of the 9 treatments were economically dominated and only 3 treatments are potentially cost-effective depending on patient's willingness to pay for the considered outcomes: medical management (MM) + placebo, MM + naltrexone, and MM + naltrexone + acamprosate.

**Conclusions:** Few studies consider the patient's perspective in estimating costs and cost-effectiveness even though these costs may

have a substantial impact on a patient's treatment choice, ability to access treatment, or treatment adherence. For this study, the choice of the most cost-effective treatment depends on the value placed on the outcomes by the patient, and the conclusions drawn by the patient may differ from that of the provider/payer.

**Key Words:** alcohol treatment, cost-effectiveness, patient costs

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Most cost and cost-effectiveness studies of substance use treatment focus on the provider's/payer's costs. Although this perspective is important (especially for government policy makers and third-party payers such as private health insurance), the costs incurred by patients should also be considered when evaluating alternative treatments to ensure that these options are cost-effective for patients as well as for providers. Treatment costs may be substantial to the patient and may affect a patient's ability to seek treatment or to fully complete a treatment regimen. Several studies have examined the factors associated with an individual's decision to seek alcohol treatment,<sup>1–3</sup> and among these factors are the perceived costs and benefits of the treatment.<sup>1,4</sup>

Unfortunately, collecting patient cost data can be challenging, and to date few economic evaluations of health care have done so. A small body of literature examining cancer care and screening have found that patient costs significantly contribute to the overall costs of care.<sup>5–8</sup> To our knowledge, no study has examined the cost-effectiveness of substance use treatment from the patient perspective, and only 1 study examines patients' costs for substance use treatment. Salome et al<sup>9</sup> found that patient time costs for substance abuse treatment were substantial (greater than 75% of the total patient costs), with out-of-pocket expenses such as travel costs and out-of-pocket fees accounting for the remainder.

The Combined Pharmacotherapies and Behavioral Interventions (COMBINE) study of 9 alcohol treatments provides a unique opportunity to estimate patient costs. The COMBINE study not only collected data on provider/payer costs but also economic data for patients including wage data and time spent participating in treatment. We use these data

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combined with other information collected as part of the larger study to estimate patient costs and to evaluate the cost-effectiveness of the 9 COMBINE treatments from the patient perspective.

## COMBINE STUDY DESIGN

The COMBINE study design has been described previously.<sup>10–12</sup> Briefly, COMBINE randomly assigned 1383 eligible alcohol-dependent individuals to 1 of 9 treatments for 16 weeks of outpatient treatment. Participants in 8 of these treatments received up to 9 sessions of medical management (MM) delivered by medically trained providers that focused on improving medication adherence and alcohol abstinence. Patients in these treatments received either naltrexone (active or placebo), acamprosate (active or placebo), or both naltrexone and acamprosate. Participants in 4 of the 8 treatments also received up to 20 sessions of more intensive cognitive behavioral therapy (combined behavioral intervention [CBI]) delivered by alcoholism treatment specialists. A ninth treatment group received CBI only with no medication or MM sessions. In addition, participants across all treatments were encouraged to attend local self-help recovery meetings (eg, Alcoholics Anonymous).

Participants underwent assessments at baseline, at each MM session, and at weeks 8 and 16. MM sessions consisted primarily of biologic assessments and discussions of alcohol effects on the body and information about how the medications work. Assessments at baseline and at weeks 8 and 16 included more indepth data collection including patient surveys that collected data on patient's time spent traveling to/from treatment sessions, wage information, and information about self-help meeting attendance.

## METHODS

### Cost Analysis

To compute patients' costs associated with the COMBINE treatments, we followed the microcosting approach used by Zarkin et al<sup>13</sup> in estimating COMBINE providers'/payers' costs. We estimated each patient's treatment cost as the value of the patient's time spent participating in treatment and self-help recovery programs, including travel to/from the session/meeting site. We also estimated the patient's out-of-pocket expenses for medication costs (expected prescription copayments) and out-of-pocket expenses for session visits (expected office visit copayments). Our approach presents a lower bound of patient costs because it does not include other potential costs such as out-of-pocket transportation expenses (eg, bus fare) or other expenses (eg, child care). These additional expenses and their frequency of occurrence were not collected as part of the COMBINE study; however, time typically accounts for the majority of patient costs,<sup>8,9</sup> so our time cost estimates should represent the largest share of patient costs.

### Patient Time Costs

Because COMBINE was a research study, we wanted to estimate treatment costs that would be incurred in real-world settings (as opposed to those required to implement a

clinical trial research protocol). Zarkin et al<sup>14</sup> identified COMBINE activities that would be needed to implement the therapies in clinical practice, and we used this classification in calculating the patient time.

The actual time spent by patients receiving a treatment session (MM and CBI) and the number of sessions received over the 16-week period were collected in the study's Coordinating Center Data Management System (DMS).<sup>14</sup> Time spent in assessments was reported by the project coordinator on the Project Coordinator's Resource Allocation Worksheet (PC-RAW).<sup>14</sup> The Project Coordinator's Resource Allocation Worksheet captured an estimate of the clinical staff and patient time spent on clinically relevant assessment activities. Because this estimate was not patient-specific we used the median time calculated across clinic sites as the patient's time receiving the assessment. The number of assessments received by the patient was recorded in the Data Management System. We used patients' self-reported data on time spent traveling to/from the clinic site and patient wage data collected in the Form 90 Economic Data (Form 90 ED). Self-reported patient time for self-help program participation (travel and session time) also was collected in the Form 90 ED. The Form 90 ED is a modified version of the Form 90 family of instruments that collects self-reported alcohol use and economic outcome data for alcohol treatment studies.<sup>15–18</sup> For the COMBINE study, Form 90 ED was administered to patients at intake and at 8 and 16 weeks postintake.

We standardized patients' time costs by using the average hourly wage calculated across all patients in all treatments as the unit price for time. This standardization helped eliminate geographic variation in hourly wages due to cost-of-living differences, and it mitigated the effect of wage outliers across treatments. As part of our sensitivity analysis, we estimated costs using each patient's actual wage as the unit price for time faced by that patient.

For each patient, the patient time cost associated with an activity (eg, treatment sessions, clinical assessments, self-help meetings) is the product of the time spent in that activity and the average hourly wage rate, which is then summed over all activities. The patient's travel time cost is the product of the average time reported traveling for each session/meeting across the 3 data collection points (intake, 8 and 16 weeks postintake) and the average hourly wage. This cost is then multiplied by the number of sessions/meetings that the patient attended. If an MM and CBI session occurred on the same day, travel costs were only applied once for that day. Summing the total activity costs and the total travel costs yields the total patient time cost associated with treatment.

### Patient Costs for Medication

For our main analysis, we assumed that patients had prescription drug coverage through private health insurance. We examined the formularies of several large health insurance companies in the United States and we found that, if covered, naltrexone is typically covered in its generic form (lower copay) and acamprosate is typically covered as a preferred drug in its brand form of Campral (higher copay). Therefore, we assumed a generic copay of \$11 for a 30-day prescription of naltrexone and a preferred-brand copay of \$25

for a 30-day prescription of acamprosate. These copay amounts were based on average copay amounts from the 2005 Kaiser/HRET Employer Health Benefit Survey<sup>19</sup> and updated to 2007 dollars using the medical Consumer Price Index (CPI).

As part of our sensitivity analysis, we estimated a scenario in which we assumed that naltrexone and acamprosate have the same generic brand copay of \$11 per 30-day prescription.

### Patient Costs for Session Visits

For our main analysis, we assumed that patients had health insurance coverage for treatment sessions. According to the Insurance Component of the 2005 Medical Expenditure Panel Survey, the average dollar copay for a doctor visit is \$20 (adjusted to 2007 dollars),<sup>20</sup> and we used this amount for each session visit. The total out-of-pocket expense for each patient is the product of the copayment amount and the number of sessions attended by the patient.

For our sensitivity analysis, we estimated patients' costs under the assumption that patients had no insurance coverage and must bear the full cost of their treatment. For this scenario, we used the average wholesale price published in *Red Book*<sup>21</sup> for pharmaceutical costs for acamprosate and naltrexone. The average wholesale price is in most cases the manufacturer's suggested average wholesale price, and it is often higher than the price that large purchasers normally pay.<sup>13</sup> The average wholesale price is also the most commonly used price index in pharmaceutical transactions.

The average wholesale prices of acamprosate and naltrexone are \$0.74 per 333 mg tab and \$4.29 per 50 mg tab, respectively, which for this study translates into a daily cost of \$6.67 for acamprosate (\$200 for a 30-day supply) and \$8.58 for naltrexone (\$257 for a 30-day supply). We assumed a charge of \$71 per MM session and \$105 per CBI session. Our estimates were derived from data on MM and behavioral therapy sessions presented by Dewan<sup>22</sup> and updated to 2007 dollars using the medical Consumer Price Index. These esti-

mates represent the full charge that the patient is billed by the doctor's office and is usually greater than the actual costs of the care received because it includes fee income.

### Effectiveness Measures

Following the COMBINE efficacy study,<sup>10</sup> the effectiveness outcomes selected for this analysis are proportion of patients with good clinical outcomes (defined as abstinent or moderate drinking without problems with moderate drinking defined as a maximum of 11 (women) and 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<sup>23</sup> assessing physical, social, and psychological consequences of drinking) at 16 weeks,<sup>24</sup> proportion of patients that do not return to heavy drinking (defined as  $\geq 5$  standard drinks per day for men and  $\geq 4$  standard drinks per day for women) within the 16-week treatment period, and percent days abstinent from alcohol within the 16-week period. The good clinical outcome measure combines alcohol use and alcohol-related problems. Patients may have moderate drinking episodes but still have a good clinical outcome, provided the episodes did not lead to other physical, social, or psychologic problems. This measure may be valued by many patients as the best overall reflection of alcohol problem resolution. The dichotomous measure that assesses whether any heavy drinking occurred during the follow-up identifies high severity drinking episodes but does not indicate how often they may have occurred and does not pick up episodes of moderate drinking. This measure may be important to patients who do not have a goal of abstinence but rather want to limit the amount of alcohol they consume at any 1 sitting. Finally, percent days abstinent provides a continuous measure of drinking frequency during the follow-up but does not differentiate between days with light or moderate drinking and days on which large quantities of alcohol are consumed (ie, "binges"). Percent days abstinent

TABLE 1. Mean Patient Time (in Hours) for 16-Week Treatment

Treatment Arm	N	Total Patient Time*	Total Time in Assessments*†	Total Time in MM/CBI Sessions		Total Time in Self-Help Meetings	Total Travel Time**
				MM	CBI		
MM + placebo	153	30.34 (2.60)	4.47 (0.02)	3.14 (0.08)	—	8.07 (1.75)	14.65 (1.12)
MM + naltrexone	154	32.60 (3.31)	4.44 (0.02)	3.06 (0.10)	—	10.72 (2.25)	14.39 (1.22)
MM + naltrexone + acamprosate	148	31.30 (3.02)	4.42 (0.02)	3.00 (0.09)	—	9.31 (1.85)	14.56 (1.31)
CBI only	155	34.85 (3.05)	3.91 (0.01)	—	8.69 (0.36)	5.97 (1.71)	16.28 (1.52)
MM + acamprosate	151	33.73 (4.29)	4.43 (0.02)	3.07 (0.09)	—	9.38 (2.30)	16.84 (2.44)
MM + placebo + CBI	156	44.64 (2.52)	4.65 (0.03)	3.09 (0.08)	9.02 (0.33)	7.41 (1.44)	20.46 (1.36)
MM + naltrexone + CBI	154	44.88 (2.82)	4.65 (0.02)	3.10 (0.08)	8.90 (0.30)	9.15 (1.82)	19.08 (1.13)
MM + naltrexone + acamprosate + CBI	157	43.07 (2.96)	4.57 (0.03)	2.90 (0.09)	8.18 (0.35)	9.06 (1.84)	18.35 (1.42)
MM + acamprosate + CBI	151	46.38 (3.60)	4.63 (0.03)	3.06 (0.09)	8.56 (0.35)	9.30 (1.79)	20.82 (2.07)
All treatments <sup>§</sup>	1379	38.02 (1.08)	4.47 (0.01)	3.05 (0.03)	8.67 (0.15)	8.70 (0.62)	17.28 (0.53)

Standard errors in parentheses.

\*Mean patient times are statistically significantly different across all treatment arms at the 0.01 level by analysis of variance across treatment arms.

†Assessments include assessments at baseline and those vitals/blood alcohol content readings taken at treatment sessions.

\*\*Total travel time includes travel to and from MM sessions, CBI sessions, and self-help program meetings.

§Mean session times for "All Treatments" are conditional on treatment arms that provided the relevant service.

MM indicates medical management; CBI, combined behavioral intervention.

may be of interest to patients who have a goal of reducing the frequency of drinking.

These outcomes are the same as those analyzed in Zarkin et al<sup>13</sup> and similar to the primary outcomes from Anton et al<sup>10</sup>. As in the main findings paper<sup>10</sup> and the provider/payer-perspective cost-effectiveness study,<sup>13</sup> all outcomes were adjusted for baseline percent days abstinent and clinic site.

### Cost-Effectiveness Analysis

The first step in the cost-effectiveness analysis was to rank the treatments in increasing order of mean per-patient cost for each of the effectiveness measures. Incremental cost-effectiveness ratios (ICER<sub>ij</sub>), defined as (C<sub>j</sub>-C<sub>i</sub>)/(E<sub>j</sub>-E<sub>i</sub>) where condition j is the next most costly treatment compared with i, were then computed for each treatment relative to the next most costly option after eliminating treatments that are economically dominated by other treatments.<sup>25</sup>

A treatment is eliminated from the cost-effective choice set through strict dominance if another treatment is less costly and more effective than the eliminated treatment. A treatment is eliminated through extended dominance if it has a greater ICER than a more costly treatment.<sup>26</sup> In that case, the cost of achieving a given level of the outcome is lower if the dominated treatment is eliminated. The nondominated treatments that remain comprise the cost-effectiveness frontier (CEF), which represents the maximum attainable effectiveness for a given cost level. ICERs are computed and reported for each treatment on the CEF.

We calculated cost-effectiveness acceptability curves (CEACs) to reflect sampling variability in our analysis. CEACs quantify and graphically represent uncertainty in economic evaluations of health care.<sup>27-29</sup> CEACs incorporate the inherent variability of the cost and effectiveness estimates and show the probability that a treatment is the cost-effective option compared with the alternatives as a function of the patient's willingness to pay for the outcome. Willingness to pay refers to the value that a person is willing to pay to achieve a given health outcome.<sup>30</sup> We used nonparametric bootstrap methods to calculate CEACs.

### RESULTS

As shown in Table 1, the average total patient time ranged from about 30 hours to 46 hours for the 16-week trial. Time spent traveling to/from treatment sessions and self-help program meetings accounted for the largest portion of patient time.

MM + placebo (although no cost was attributed to the placebo, MM sessions involve an active intervention) is the least costly treatment from the patient's perspective (\$904 per patient), and MM + acamprostate + CBI is the most costly (\$1592 per patient) (Table 2). Travel time costs accounted for the largest component of costs across all treatments, and medication prescription copayments contributed the least to total patient costs.

Table 3 reports the mean total costs and effectiveness for each outcome followed by the resulting ICER. For all outcomes, MM + placebo is the least costly treatment from the patient perspective and therefore remains on the CEF; however, MM + placebo also has the smallest mean effec-

TABLE 2. Mean Patient Costs by Treatment Arm

Treatment Arm	N	Total Cost of Treatment*	Cost of Medication (Copays)**	Cost of Office Visits (Copays)**	Assessment Time Cost\$	Session Time Cost		Self-Help Program Time Cost	Total Travel Cost*†
						MM	CBI		
MM + placebo	153	\$904.47 (64.97)	—	\$151.18 (3.35)	\$110.97 (0.49)	\$78.07 (2.09)	—	\$200.43 (43.34)	\$363.81 (27.82)
MM + naltrexone	154	\$996.50 (83.45)	\$40.29 (1.43)	\$146.73 (3.99)	\$110.28 (0.58)	\$75.85 (2.50)	—	\$266.16 (55.83)	\$357.19 (30.21)
MM + naltrexone + acamprostate	148	\$1046.21 (75.82)	\$125.30 (4.63)	\$143.87 (4.02)	\$109.82 (0.59)	\$74.39 (2.20)	—	\$231.22 (45.92)	\$361.60 (32.46)
CBI only	155	\$1060.11 (78.37)	—	\$194.77 (7.77)	\$97.06 (0.33)	—	\$215.83 (9.03)	\$148.32 (42.46)	\$404.13 (37.68)
MM + acamprostate	151	\$1067.34 (107.93)	\$84.93 (3.04)	\$145.07 (3.96)	\$110.04 (0.58)	\$76.27 (2.28)	—	\$232.83 (57.05)	\$418.20 (60.56)
MM + placebo + CBI	156	\$1468.32 (66.38)	—	\$359.92 (9.64)	\$115.48 (0.63)	\$76.78 (2.06)	\$224.04 (8.24)	\$184.08 (35.83)	\$508.02 (33.85)
MM + naltrexone + CBI	154	\$1512.36 (73.67)	\$43.07 (1.36)	\$354.96 (8.74)	\$115.48 (0.62)	\$76.99 (1.91)	\$221.02 (7.46)	\$227.25 (45.23)	\$473.59 (28.04)
MM + naltrexone + acamprostate + CBI	157	\$1524.79 (79.05)	\$125.37 (4.86)	\$330.17 (10.76)	\$113.56 (0.74)	\$72.02 (2.17)	\$203.08 (8.59)	\$224.94 (45.73)	\$455.65 (35.32)
MM + acamprostate + CBI	151	\$1592.46 (94.55)	\$95.03 (3.07)	\$346.04 (9.98)	\$115.03 (0.66)	\$75.97 (1.97)	\$212.41 (8.67)	\$230.98 (44.41)	\$517.00 (51.47)
All treatments <sup>§</sup>	1379	\$1242.92 (28.32)	\$85.51 (1.80)	\$242.21 (3.60)	\$110.86 (0.24)	\$75.79 (0.76)	\$215.26 (3.76)	\$216.05 (15.49)	\$429.12 (13.21)

Standard errors in parentheses.

\*Mean patient costs are statistically significantly different across all treatment arms at the 0.01 level by analysis of variance across treatment arms.

†For our baseline cost estimates, we assumed a copy of \$11 for a 30-day prescription of naltrexone and \$25 for a 30-day prescription of acamprostate.

‡For our baseline cost estimates, we assumed a copy of \$19.77 for MM and CBI office visits.

§Assessments include assessments at baseline and vitals/blood alcohol content readings taken at relevant treatment visits.

¶Total travel cost includes time spent in travel to and from MM sessions, CBI sessions, and self-help program meetings. It excludes out-of-pocket expenses (eg fuel expense, bus fare) associated with travel.

‡‡Mean costs for "All Treatments" are conditional on treatment arms that provided the relevant service.

‡‡‡MM indicates medical management; CBI, combined behavioral intervention.

TABLE 3. Incremental Cost-Effectiveness Ratios

Treatment Arm	Mean Cost	Proportion With Good Clinical Outcomes		Proportion That Avoid Heavy Drinking		Percent Days Abstinent	
		Mean Effectiveness	Incremental CE Ratio ( $\delta C/\delta E$ , \$)*	Mean Effectiveness	Incremental CE Ratio ( $\delta C/\delta E$ , \$)†	Mean Effectiveness	Incremental CE Ratio ( $\delta C/\delta E$ , \$)‡
MM + placebo	\$904.47 (64.97)	0.58 (0.04)	—	0.26 (0.03)	—	73.8 (2.32)	—
MM + naltrexone	\$996.50 (83.45)	0.74 (0.04)	\$575.19	0.35 (0.04)	\$1022.56	80.0 (2.01)	\$14.84
MM + naltrexone + acamprosate	\$1046.21 (75.82)	0.78 (0.04)	\$1242.75	0.39 (0.04)	\$1242.75	80.5 (1.90)	\$99.42
CBI only	\$1060.11 (78.37)	0.61 (0.04)	Dominated	0.24 (0.04)	Dominated	66.7 (2.55)	Dominated
MM + acamprosate	\$1067.34 (107.93)	0.61 (0.04)	Dominated	0.33 (0.04)	Dominated	75.6 (2.20)	Dominated
MM + placebo + CBI	\$1468.32 (66.38)	0.71 (0.04)	Dominated	0.31 (0.04)	Dominated	79.8 (2.03)	Dominated
MM + naltrexone + CBI	\$1512.36 (73.67)	0.75 (0.04)	Dominated	0.34 (0.04)	Dominated	75.9 (2.26)	Dominated
MM + naltrexone + acamprosate + CBI	\$1524.79 (79.05)	0.74 (0.04)	Dominated	0.28 (0.04)	Dominated	77.6 (2.26)	Dominated
MM + acamprosate + CBI	\$1592.46 (94.55)	0.75 (0.04)	Dominated	0.35 (0.04)	Dominated	78.3 (2.05)	Dominated

\*ICER is dollars (\$) per patient achieving a good clinical outcome.

†ICER is dollars (\$) per patient avoiding a return to heavy drinking.

‡ICER is dollars (\$) per patient for a percentage point increase in percent days abstinent.

MM indicates medical management; CBI, combined behavioral intervention.

tiveness for all outcomes. MM + naltrexone (MM + N) and MM + naltrexone + acamprosate (MM + N + A) are more costly but yield greater mean effectiveness and are also on the CEF. All the remaining treatments are strictly economically dominated because they are more costly and have smaller mean effectiveness compared with MM + N and MM + N + A.

The cost-effectiveness results for all 3 outcomes indicate that only MM + placebo, MM + N, and MM + N + A are potentially cost-effective depending on patient's willingness to pay for the outcomes. The ICER moving from MM + placebo to MM + N is \$575 per patient achieving a good clinical outcome, \$1023 per patient avoiding a return to heavy drinking, and \$15 per patient for a percentage point increase in percent days abstinent (A percentage point increase in percent days abstinent may not be clinically meaningful because 1% represents less than 1 day. Instead, if we consider days as our unit, 1 additional day of abstinence per month [3.3 percentage point increase] would be associated with an ICER moving from MM + placebo to MM + N of approximately \$50 [ $\$15 \times 3.3$ ]). The ICER moving from MM + N to MM + N + A is \$1243 per patient achieving a good clinical outcome, \$1243 per patient avoiding a return to heavy drinking, and \$99 per patient for a percentage point increase in percent days abstinent.

For good clinical outcomes (Fig. 1A), MM + placebo has the highest probability of being the most cost-effective for small willingness to pay (WTP) values (<\$500). MM + N has the highest probability of being the most cost-effective for WTP values between about \$500 and \$1000. MM + N + A has the highest probability of being the most cost-effective for WTP values greater than \$1000, although this probability does not exceed 75%. All other treatments have extremely low probabilities of being optimal.

Similar results are found for avoiding return to heavy drinking (Fig. 1B). Again, MM + placebo has the highest probability of being the most cost-effective for small WTP

values. MM + N + A has the highest probability of being the most cost-effective for WTP values greater than \$1000. For percent days abstinent (Fig. 1C), MM + N + A has the highest probability of being the most cost-effective for WTP values above \$50, although this probability never exceeds 60%.

### Sensitivity Analysis

For our sensitivity analyses, we considered 2 alternative scenarios regarding patients' insurance coverage (full results available on request). First, we allowed a generic drug option for acamprosate and naltrexone so that the prescription copay is the same for both drugs. Next, we estimated a scenario in which patients do not have any insurance coverage and must bear the full treatment costs. For each of these scenarios, we only examined the effect on costs and the subsequent cost-related effect on the cost-effectiveness ratios. Because we did not actually observe patients under these scenarios, we were unable to collect effectiveness data within each scenario, and therefore we assumed no change in treatment effectiveness.

Under these scenarios, MM + placebo, MM + N, and MM + N + A remain on the CEF as viable options. Compared with the main analysis, our first scenario (generic drug option for both drugs) yields slightly lower costs for treatments that include acamprosate. Because of these lower costs, MM + N + A has the highest probability of being the most cost-effective except at small WTP values. Thus, if patients face similar costs for naltrexone and acamprosate, then it appears that most patients would opt for MM + N + A as the preferred treatment.

Our second scenario (no insurance coverage) yields greater costs for patients compared with the main analysis. MM + placebo (the least costly treatment) has the highest probability of being the most cost-effective treatment at much greater WTP values compared with the main analysis. MM + N and MM + N + A do not have the highest probability of

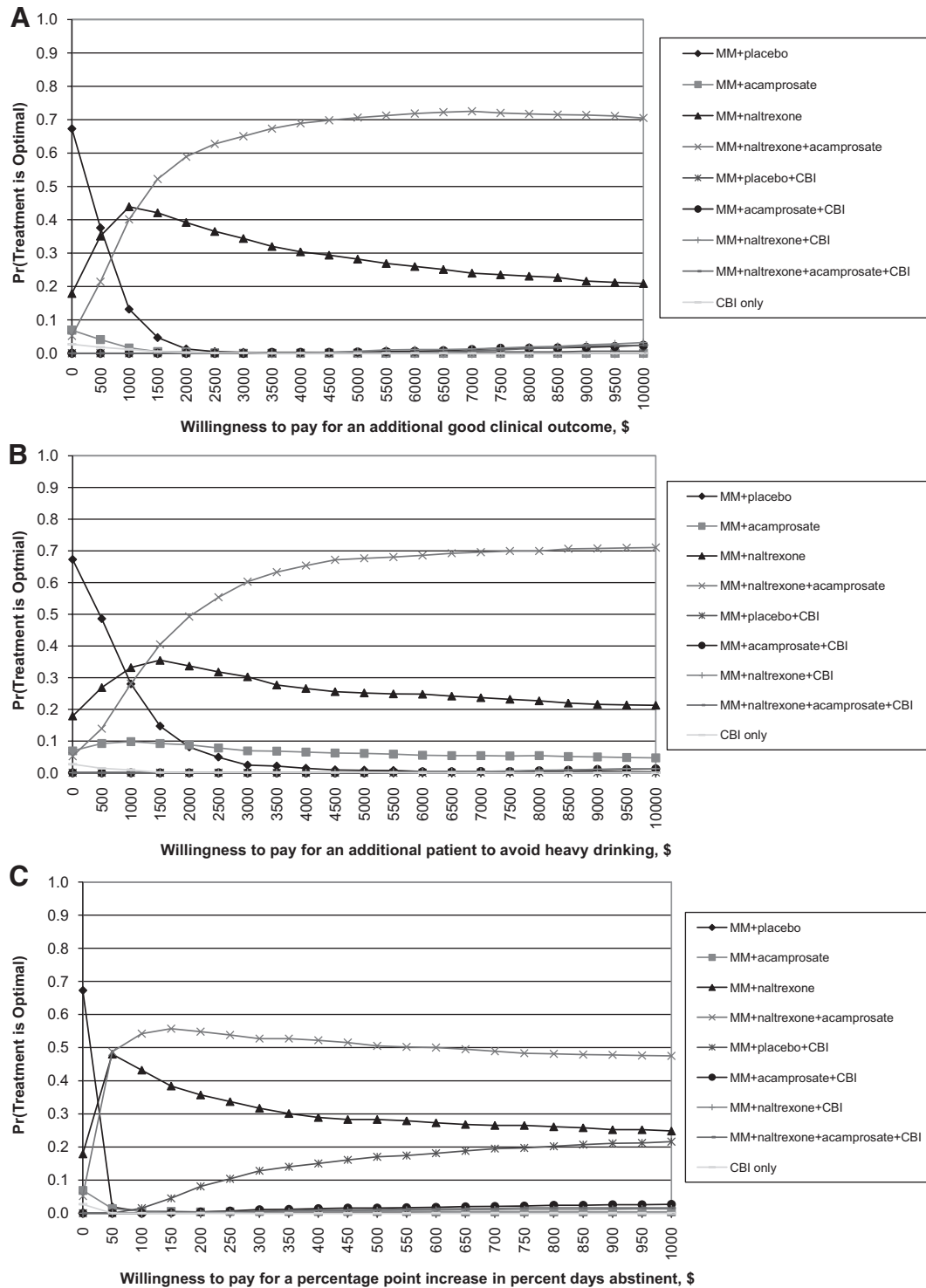


FIGURE 1. Cost-Effectiveness Acceptability Curves.

being the most cost-effective treatment except at much greater WTP values. This scenario demonstrates that the costs faced by the patient can greatly affect their conclusions regarding the optimal treatment option.

Finally, we also conducted a sensitivity analysis on our use of the average wage as the unit price for patient time. We

estimated each patient’s cost using their reported wage rather than the average wage calculated over all patients. This analysis shows that patient costs and the cost-effectiveness analysis are sensitive to the observed geographic differences and outliers in our patient-reported wages. MM + N replaces MM + placebo as the least costly treatment, and therefore

MM + placebo is strictly dominated. MM + N and MM + N + A are the only 2 treatments on the CEF. Given that MM + placebo is not a practical clinical option, the relevant choice set in our analysis does not change for patients.

## DISCUSSION

This article presents the first cost and cost-effectiveness study from the patient perspective of pharmaceutical and behavioral treatments for alcohol dependence. No previous studies of alcohol treatment costs have specifically examined the costs incurred by patients and thus are limited in their ability to inform policy makers about how these treatments may impact patients. Patient costs should not be ignored or considered as trivial because they may affect a patient's ability to undergo treatment or to fully follow a prescribed treatment plan.

The cost analysis reveals that patients incur significant costs to participate in clinical care and also devote significant time and resources to access care (eg, travel time) and participate in self-help programs. The cost analysis offers a striking view of the cost associated with self-help program attendance, one that runs counter to conventional wisdom that mutual-help participation is free and readily accessible.

The results of the cost-effectiveness analysis show that only 3 of the 9 COMBINE treatments are cost-effective choices for patients: MM + placebo, MM + N, and MM + N + A. As noted in Zarkin et al,<sup>13</sup> the statistical tests in Anton et al<sup>10</sup> were the clinical study's prespecified analysis of variance-type tests of main effects and interactions. These tests did not find a benefit for acamprosate either as a main effect or in 2- or 3-way interactions. Pairwise comparisons, such as between MM + N and MM + N + A were not examined. In contrast, Zarkin et al<sup>13</sup> and the study presented here performed prespecified pairwise comparisons for the cost-effectiveness analysis to examine each treatment relative to every other treatment. The pairwise comparisons presented in Zarkin et al<sup>13</sup> and here are not formal statistical tests; on efficacy alone, MM + N + A is not significantly better than MM + N.<sup>10</sup> However, based on the joint distribution of patient cost and effectiveness, MM + N + A is a potentially cost-effective choice that may be selected by patients under certain circumstances. The patient's choice between MM + N and the more effective and more costly MM + N + A depends on whether the cost of the incremental increase in effectiveness is worth it to the patient.

Our results show that the provider/payer perspective and the patient perspective may differ. As presented in Zarkin et al,<sup>13</sup> the provider/payer perspective indicates that MM + N has the highest probability of being the most cost-effective treatment for WTP values up to about \$7000 to \$7500 for good clinical outcomes and avoiding heavy drinking. From the patient perspective, MM + N has the highest probability of being the most cost-effective treatment for these 2 outcomes only up to a WTP value just below \$1500. Beyond this WTP value, MM + N + A has the highest probability of being the optimal choice. Between WTP values of \$1500 and \$7000, providers/payers and patients may draw different conclusions regarding the optimal treatment. Thus, this study

highlights 2 key issues: (1) provider/payer and patient may have different WTP for a given outcome; and (2) for the same WTP value, the provider/payer and patient may draw different conclusions. As shown here, completely different conclusions about the optimal treatment may be drawn depending on one's perspective. This finding raises questions as to whether this difference between patient and provider/payer preferences might lead to a less than optimal choice set for patients; that is, would a provider/payer offer a treatment that they conclude is not an optimal choice even if it might be the preferred choice for patients? However, patients do not provide treatment, so this difference may always exist. The challenge remains for policy makers to determine policies that help align the preferences of these 2 key decision makers.

Our study has a few limitations that should be noted. Because MM + placebo is not available clinically and MM was not evaluated in the absence of a placebo, we cannot determine the impact of MM alone. Our patient cost analysis relies on patient self-reported data regarding average time spent traveling to and from sessions. As with most self-reported data, these data may suffer from recall bias leading to an under- or overestimation of travel time.<sup>31</sup> Furthermore, because this was a research study, patients were required to receive sessions from 1 of 11 clinic sites. In a real-world setting, patients may be able to access treatment providers that are closer to them.

Another limitation is that we only have data on patient time and wages, and we estimated coinsurance copayments based on national averages. COMBINE trial participants received prescription drugs and treatment sessions free-of-charge, and data were not collected on out-of-pocket expenses that might be incurred in a real-world setting (eg, coinsurance, travel expenses). Because patient time represents the majority of cost, any estimation error due to our assumptions about insurance coverage should have a small effect on the results.

Furthermore, we do not take into account full patient preferences and the benefits and costs associated with other treatment attributes beyond patients' time and selected out-of-pocket treatment expenses. For example, patients' attitudes and preferences may differ regarding medication side effects, aversion to taking medication, or participation in behavioral therapy.

Finally, although we use activities identified as best clinical practice,<sup>14</sup> the treatment regimen we use in our costing algorithm follows the COMBINE protocol. As noted by Zarkin et al,<sup>13</sup> patients probably are seen more frequently in a clinical trial compared with best clinical practice, so in this case we expect our patient cost estimates to represent upper bounds of the actual best practice treatment costs for patients. Furthermore, if patients are required to partially or fully pay for medication and session visits, these costs may inadvertently create an economic barrier to treatment and adversely affect session attendance or adherence to medication regimens. We do not fully observe the relationship between patient behavior and expected out-of-pocket costs within the COMBINE trial, and therefore we cannot test

how this relationship might affect patient adherence and overall costs.

Notwithstanding these limitations, our study makes an important contribution to the literature because it provides an economic analysis of the COMBINE therapies from the patient perspective and it provides quantitative evidence of the impact that perspective can have on conclusions about alternative treatment options. For this study, the choice of the economically optimal treatment depends on the value placed on the outcomes by the patient rather than the provider/payer, and as we have shown the conclusions drawn by the patient may differ significantly from that of the provider/payer.

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