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Meta-Analysis of Supplemental Treatment for Depressive and Anxiety Disorders in Patients being Treated for Alcohol Dependence

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Abstract

Approximately half of those receiving treatment for an alcohol use disorder (AUD) also suffer with an anxiety or depressive ("internalizing") disorder. Because all internalizing disorders mark a poor alcohol treatment outcome, it seems reasonable to supplement AUD treatment with a psychiatric intervention when these disorders co-occur with AUD. However, this conclusion may be faulty given that the various possible inter-relationships between AUD and internalizing disorders do not uniformly imply a high therapeutic yield from this approach. Unfortunately, the studies conducted to date have been too few and too small to resolve this important clinical issue with confidence. Therefore, we used a meta-analytic method to synthesize the effects from published randomized controlled trials (RCTs) examining the impact of supplementing AUD treatment with a psychiatric treatment for co-occurring internalizing disorder (N=15). We found a pooled effect size (d) of .32 for internalizing outcomes and .22 for a composite of alcohol outcomes; however, the alcohol outcomes effect sizes were greater than this for some specific outcome domains. Subgroups that differed in terms of internalizing outcomes included treatment type (medication vs. CBT) and treatment focus (anxiety vs. depression). There was also a trend for the studies with better internalizing disorder outcomes to have better alcohol outcomes. These results indicate that clinical outcomes (both psychiatric and alcohol-related) could be somewhat improved by supplementing AUD treatment with psychiatric treatment for co-occurring internalizing disorder.

INTRODUCTION

Anxiety and depressive disorders (referred to collectively as "internalizing" disorders) co-occur with alcohol use disorders (AUDs) at a rate that far exceeds chance.[1–5] This association is especially pronounced in AUD treatment settings where about 50% of patients have a co-occurring internalizing disorder.[6,7] Lending clinical importance to this association is the negative prognostic information that internalizing disorders convey in terms of AUD course and response to treatment.[6,8–14] For example, AUD treatment patients with a co-occurring internalizing disorder have approximately double the risk of relapsing to alcohol use in the months following treatment compared to those with no internalizing disorder.[6,15]

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Declaration on Interests
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

However, it does not necessarily follow that the addition of an internalizing treatment component would improve alcoholism treatment outcomes for these individuals.

A small number of randomized controlled studies have been conducted assessing various psychiatric treatments for internalizing disorders in AUD treatment patients.[12,16–24] Unfortunately, it is difficult to draw firm conclusions from this body of work since the findings are quite mixed. For example, Kushner and colleagues[17] found that psychiatric treatment benefited both co-occurring internalizing disorder and AUD outcomes. Randall and colleagues.[22] found that psychiatric treatment benefited neither co-occurring internalizing disorder nor AUD outcomes. Schade and colleagues[25] found that psychiatric treatment improved co-occurring internalizing disorder but not AUD outcomes. Beyond the obvious difficulty of drawing conclusions from such mixed findings is the problem that no single study examining this question to date includes an adequate sample size and the other methodological qualities needed to establish its findings as definitive. Meta-analysis offers a practical solution to the dilemma of interpretation posed by the availability of several small studies with mixed findings in the absence of a single substantial study that could be considered definitive.[26,27]

To date, two quantitative reviews of this literature have been reported in the literature. Tiet and Mausbach[28] calculated and reported the effect size from studies examining the clinical benefit resulting from adding psychiatric treatment for a variety of psychiatric disorders (e.g., depression, anxiety, bipolar, schizophrenia, “other”) in substance use disordered patients. While offering advantages over purely qualitative reviews, the capacity of this review to render the information from the available studies into maximally informative conclusions is limited by several design features. Unlike a standard meta-analysis, they did not empirically integrate effect sizes across studies into one omnibus index of effect. Further, they did not limit studies to randomized controlled trials. That review also failed to distinguish among potentially important between-study differences such psychosocial treatments versus pharmacological treatments. In the only other quantitative review of this literature, Nunes and Levin[29] did conduct a formal meta-analysis, but one that was limited to pharmacological treatments of depression in substance abusing populations. As we argue in greater detail below, however, ignoring studies using psycho-social treatments, failing to distinguish between AUD and other addictive disorders and failure include internalizing disorders beyond depression are all significant limitations in a review of this literature.

In the present work, we sought to refine and extend the reviews cited above to further clarifying the clinical value of supplementing AUD treatment with a specific treatment for co-occurring internalizing disorder. We began by identifying all published randomized controlled studies evaluating the impact of supplemental anxiety and depression treatment in comorbid AUD treatment patients. We chose to examine both depression and anxiety in this review based on the growing literature suggesting that both syndrome types share symptoms, underlying psychopathological processes, genetic vulnerabilities and associations to alcohol disorder.[30–34] Further, we include studies using both psycho-social and pharmacological treatments. This is important because substance abuse treatment patients may have particular cost-benefit relationships to these treatment approaches relative to those in non-substance abusing psychiatric patients.[4,22] We also limited the studies to those that included randomized-controlled trials. Because it is well known that anxiety and depression symptoms decrease significantly following standard substance abuse treatment, and because of the likelihood of placebo effects in treating these disorders, it is critical that appropriate control groups be included.[35]

In brief, we conducted a multi-source comprehensive search of the literature to identify published studies in which patients undergoing a standard AUD treatment were randomly

assigned to also receive either a validated psychiatric treatment (medication or psycho-social) versus a control treatment for a co-occurring anxiety disorder or depressive disorder. The two core questions of interest were: 1) does psychiatric treatment for an internalizing disorder improve anxiety/depression outcomes in AUD treatment patients? and, 2) does psychiatric treatment for a co-occurring internalizing disorder improve AUD treatment outcomes? We also explored subgroup variables including type of psychiatric treatment (medication vs. psycho-social) and type of internalizing disorder (anxiety vs. depression). We predicted, based upon our earlier work cited above, that supplemental psychiatric intervention would demonstrate clinical benefits for both internalizing and AUD outcomes.

METHOD

Inclusion Criteria

Sample Characteristics—Individuals included were: 1) at least 18 years of age; 2) diagnosed with current DSM (edition III or later) alcohol dependence or alcohol abuse; 3) currently a patient in an AUD treatment program; and, 4) diagnosed with any current DSM (edition III or later) anxiety disorder (except simple phobia, PTSD, and OCD) or were experiencing a current DSM (edition III or later) depressive disorder, including major depression, dysthymia and depression NOS. The majority of studies included with a focus on depressive disorder included patients exclusively with a diagnosis of major depression (97% all depressed patients included in the meta-analysis). Of the two studies that included depressive disorders other than major depression, one reported 98% with major depression and 2% with dysthymia.[36] The other, reported 72% with major depression and the remainder with either dysthymia or depressive disorder NOS (breakdown of the latter two groups was not provided).[37] Note that all studies included indentified depressed patients based on DSM criteria except for one that used a clinical cut-off score on a measure of depression.[38] Individuals in that study had a mean score for both the Beck Depression Inventory and Hamilton Depression interview of 20, indicating a clinically significant depression on both measures.

Study Inclusion Characteristics—Studies that were included: 1) employed random assignment to a psychiatric treatment versus an active control condition (placebo for medication trials or therapy control for psycho-social trials) for a co-occurring internalizing disorder; 2) had a follow-up assessment within one year of treatment (where multiple follow-ups were employed, we used the earliest one); 3) included sufficient information to allow for effect sizes to be calculated for the internalizing and AUD outcome effects (however, see exceptions below); 4) were published in a peer-reviewed scientific journal; and 5) included data not published previously (this criterion was to avoid redundancy in the studies included). Of the 15 studies included, one did not report adequate information to allow for calculation of the internalizing disorder outcome effect size, but did have adequate information to calculate effect size for the alcohol outcome.[39] Three additional studies included did not report adequate information to allow for calculation of the alcohol disorder outcome effect size but did have adequate information to calculate the effect size for the internalizing disorder outcome.[40–42]

Search Strategy

Database Search—Our primary search strategy employed the OVID Medline and PsycINFO databases. We limited the search to English language articles reporting empirical studies that used human subjects. Time parameters included any indexed studies published up to the date of the initial submission of this work (June, 2010). The search logic combined three sets of general identifier types: 1) drug/alcohol (drugs other than alcohol were included in this set to ensure comprehensiveness in the initial search step); AND, 2) treatment; AND,

3) internalizing disorder. We attempted to expand each of these identifier types to include as many specific search terms as possible including those suggested by the search engine itself and in consultation with colleagues who have relevant expertise.

The search located a list of 270 research articles. We excluded 92 studies because they were duplicate citations. Another 154 studies were excluded because they were not randomized controlled trials. Of the 24 studies that remained, nine more were excluded because the population was either drug-abusing exclusively or drug and alcohol outcomes were not clearly distinguished. Nine more studies were excluded because treatment outcomes were not available in a format enabling calculation of effect sizes (however, see our attempts to obtain more information described below). One additional study was excluded because the subjects were not in an AUD treatment at the time of the study. Thus, this first search step netted five studies that were fully qualified to be included in the meta-analysis.

Additional Search Steps—The second step of the search involved examining the bibliography of studies and reviews related to the meta-analysis topic to identify relevant treatment studies that were missed by the computer-assisted database search. This step identified three additional studies that were qualified for inclusion in the meta-analysis. The second author (MGK) also identified six additional studies for inclusion based on his familiarity with the literature and field including studies from other labs that were pre-published at the time of the search. Finally, we attempted to contact by email the corresponding author of each of the nine studies excluded because data were not reported in a format allowing for conversion to effect sizes. One of the nine responded and provided additional data rendering that study eligible for inclusion. After combining results from all search steps outlined above, we identified a total of 15 studies meeting the inclusion criteria for the meta-analysis.

Characteristics of Studies Identified

Twelve of the 15 studies included tested a pharmacological treatment for the comorbid internalizing disorder and three tested a psycho-social intervention. Although we did not place limits on the type of psycho-social interventions that would be included, all three studies identified used a cognitive behavioral therapy (CBT) intervention. Six of the twelve pharmacological treatments used SSRIs, three used buspirone, two used SNDRIs, and one used a tricyclic medication. Six of the 15 studies treated a co-occurring anxiety disorder and nine treated a co-occurring depressive disorder.

Outcome Measures

One challenge of meta-analysis is to indentify the least number of outcome measures categories that can capture the range of outcome measures used. For alcohol and internalizing outcomes, we were guided by recommendations made in a recent textbook on conducting meta-analyses,[43] as well as by similar decisions made in recently published meta-analytic studies using similar populations and outcomes.[44]

Internalizing—Anxiety outcomes measures included the Hamilton Rating Scale for Anxiety (HAM-A), Social Phobia Inventory, Symptom Checklist – 90 (SCL-90), and Anxiety Discomfort Scale.[45–48] Depression outcome measures included the Hamilton Rating Scale for Depression (HAM-D), Beck Depression Inventory (BDI), Profile of Mood States (POMS) and the Montgomery and Asberg Depression Rating Scale.[49–52]

Alcohol—We identified four domains of alcohol-related outcomes including: "abstinence," "frequency," "intensity" and "quantity." Abstinence was defined as that absence of alcohol consumption during the entire follow-up period. Frequency of alcohol use included number

of drinking days, percent days drinking and percent days abstinent (reversed). Intensity of alcohol use was defined as number of heavy drinking days per week, time to first heavy drinking and percent days of heavy drinking. Quantity of alcohol use was defined as the number of drinks per drinking day, number of drinks per week and number of standard drinks per drinking day. Regarding our rationale for this approach to categorizing outcomes, we considered that abstinence is a dichotomous measure that is conceptually different from quantity, frequency and intensity of use. For the purposes of this study, we considered intensity to specifically measure *heavy* drinking. Finally, we calculated an "Overall Alcohol Outcome" for each study by averaging all the alcohol outcome effect sizes reported.

Data Reduction and Groups

Effect Size Indices—The randomized between-group factor in all cases refers to a group receiving a psychiatric treatment versus a group receiving a control/placebo treatment for an internalizing disorder. (As noted above, all patients in all studies were undergoing AUD treatment at the time of the study.) The dependent variables were outcomes for: a) the internalizing disorder; and, b) the AUD. The effect size measure we used was Cohen's d for continuous outcomes and odds ratio (OR) for categorical outcomes.[26] These effect sizes were calculated from raw data (e.g., means and standard deviations for d) when provided. When the necessary raw data were not available, effect sizes were extrapolated from ANOVA or ANCOVA data (covaried for baseline scores when available). When possible, data from intent-to-treat analyses were used. Completer data were only used when intent-to-treat information was unavailable. Where multiple post-treatment outcome time points were available in a study, we used the earliest as this provided the least variability across studies in follow-up duration.

When more than one internalizing disorder outcome measure was available in a single study, we averaged effect sizes from each measure to produce a single summary effect size for the meta-analyses. Similarly, if a study provided data on multiple alcohol outcomes domains (see above), we averaged the effect sizes to produce a single summary effect for that domain. These calculations were statistically adjusted to account for variance introduced with multiple measures.[53] Finally, to represent the overall effect size for alcohol use outcome, we averaged all of the alcohol outcome effect sizes from each study for use in the meta-analysis. (However, we also report effect sizes for each of the specific alcohol outcome measure types separately.) We treated each of the four alcohol outcome categories and the overall alcohol outcome index separately in the meta-analyses. When calculating the overall pooled effect sizes across studies (alcohol and internalizing), studies were weighted to reflect their sample size and variance.

Subgroup Analyses—In addition to examining the overall effect sizes of psychiatric treatment on internalizing and alcohol outcomes pooled across all studies, effect sizes were also calculated and compared between relevant subgroups within the pool of studies. These variables included the type of internalizing disorder treated (depression vs. anxiety) and the type of internalizing treatment (medication vs. CBT). These two subgroups were examined for both internalizing and alcohol outcomes. We also examined the influence of more effective versus less effective internalizing disorder treatment (i.e., better vs. worse internalizing disorder outcomes) on alcohol outcomes. The first two subgroup analyses are considered exploratory in nature while the last analysis is informed by our expectation that decreasing internalizing disorder symptoms contributes directly to improved AUD treatment.

Statistical Analysis

We employed the Comprehensive Meta-Analysis software 2.2 to calculate effect sizes and pooled estimates of effect across studies.[53] Random effect estimates of effect sizes are reported. The random effects model allows that the true effect may vary from study to study.[43] This is the most appropriate model, as we assume that there is heterogeneity in the samples included in the study.

To detect possible publication bias we visually examined the funnel plots for symmetry and also conducted the Egger's linear regression test and the Begg and Mazumdar rank correlation test for each outcome.[54,55] The latter two tests have been developed to examine the relation between sample size and effect size among studies included in a meta-analysis. A significant regression or correlation may suggest asymmetry in the funnel plot, which could indicate a bias in results based on sample size. In case of significant correlation or regression, we conducted the Duval and Tweedie's trim and fill analysis to provide an unbiased estimate of the pooled effect size.[56]

A test of heterogeneity of effect sizes across multiple studies was provided by the *Q* statistic. The I^2 index was also calculated to quantify the amount of heterogeneity across studies.[57] This index can be interpreted as a percentage of variability in an effect size estimate that is due to true heterogeneity versus sampling error. However, because of the relatively low number of studies included, we explored the differences in effect sizes by subgroups as described above regardless of the outcome of the overall test for heterogeneity. Subgroup indicator variables were entered in the analysis as grouping variables. For each subgroup analysis, the difference in effect sizes between the subgroups was examined by calculating the mixed-effects between-group heterogeneity ($Q_{between}$).

RESULTS

Studies Utilized

Table 1 presents descriptive for the separate studies and outcomes used in the meta-analysis. As can be seen, 14 studies provide outcome information regarding internalizing disorders. Effect sizes ranged from d= −0.025 to d= 0.785. Three studies focused on treating GAD, two studies focused on treating social phobia, and nine studies focused on treating depression. The one study that focused on treating panic disorder did not present usable outcome data for the internalizing outcome.

While 12 studies provided adequate information to calculate effect size for at least one type of alcohol outcome, fewer studies were available to calculate effects sizes for some specific alcohol outcomes. Eight studies provided adequate data for calculating outcomes indexing complete abstinence from alcohol. As shown in Table 1, OR effect sizes ranged from 0.39 to 2.83 (keeping in mind that an OR of 1 indicates no effect). Seven studies provided adequate data for calculating outcomes indexing frequency of alcohol use. As shown in Table 1, effect sizes (Cohen's $\underline{d}$) ranged from $\underline{d}$ = 0.02 to $\underline{d}$ = 0.60. Seven studies provided adequate data for calculating outcomes indexing intensity of alcohol use. The effect sizes ranged from $\underline{d}$ = −0.22 to $\underline{d}$ = 1.06. Eight studies provided adequate data for calculating outcomes indexing quantity of alcohol use. The effect sizes ranged from $\underline{d}$ = 0.08 to $\underline{d}$ = 0.72. The overall alcohol outcome effect sizes (i.e., the average effect size for all alcohol outcomes reported) were calculated separately for each of the 12 studies that contained adequate information for this analysis. The effect sizes ranged from −0.52 to 0.64.

Summary of Pooled Effects

A summary of pooled effect sizes (Cohen's d), 95% confidence intervals (CI), and heterogeneity tests for overall internalizing outcome, overall alcohol outcome, and the four alcohol outcome categories (abstinence, quantity, frequency, and intensity) are presented in Table 2.

Subgroup Analyses

Although within-group heterogeneity tests for the internalizing and alcohol outcome variables were not statistically significant (with the exception of the intensity of alcohol use outcome variable), we evaluated subgroup variables identified on an a priori basis including: a) treatment type (medication vs. CBT); b) internalizing disorder type (anxiety vs. depression); and c) internalizing outcome effect size magnitude (low vs. high) (relevant to alcohol outcomes only). For the latter variable, we dichotomized studies by splitting up those that obtained an internalizing outcome effect size that was below ("low") versus above ("high") the mean internalizing outcome effect size pooled across all the studies (i.e., d = 0.32).

Internalizing Outcomes—We tested the effects of two subgroup variables on the internalizing outcome: treatment type (CBT vs. medication) and internalizing disorder type (anxiety vs. depression). As shown in Table 3, subgroups created to represent both variables were significantly different in terms of their effect size for the internalizing outcome. For the treatment type, CBT intervention had a pooled estimate of effect size of d = 0.66, while medication yielded a smaller estimate pooled effect size of d = 0.24. Studies in which anxiety was treated also demonstrated significantly greater pooled effects sizes for the internalizing outcome (d = 0.52) than was true for studies in which depression was treated (d = 0.21).

Alcohol Outcomes—We tested the effects of three subgroup variables on the alcohol outcome: treatment type (CBT vs. medication), internalizing disorder type (anxiety vs. depression) and magnitude of the internalizing treatment effect on the alcohol outcome (low vs. high; see above). In testing these models, we used the overall alcohol outcome index for the DV as this approach allowed the maximum number of studies to be included and provided the single best estimate of drinking outcomes. As shown in Table 3, there was a trend (p = .09) for better alcohol outcomes in studies with high vs. low effect sizes on the internalizing outcomes. Also shown in Table 3 is that neither psychiatric treatment type nor internalizing disorder type impacted alcohol outcomes.

Assessment for Publication Bias

Although a visual inspection of the funnel plots revealed a roughly symmetrical pattern suggesting the absence of publication bias, we also conducted formal tests to further evaluate this potential threat to validity.[54,55] Results from the tests were not significant for the alcohol outcomes (*p*s > .05) again indicating the absence of publication bias. However, the tests were significant for the internalizing disorder outcomes (*p*s < .05).

Since the tests suggested possible publication bias for the internalizing outcome, we conducted the Duval and Tweedie trim and fill analysis on the internalizing outcome to estimate the pooled effect size after adjusting it downward with the assumption that the test identified a true publication bias.[56] The imputed random-effect effect size was d = 0.28 (95% CI, 0.12 to 0.43) for the internalizing outcome. The adjusted point estimate is fairly close to the original random effect size of 0.32 suggesting that the degree of bias inferred by the Egger's and Begg's tests was small.

DISCUSSION

We concluded from this meta-analysis that psychiatric treatments for co-occurring internalizing disorders are moderately effective in substance abusing populations and that these interventions provide a small but significant boost in the benefit of AUD treatment outcomes. This suggests that adding psychiatric treatment to existing alcoholism treatment programs is probably warranted. Given that internalizing disorders may affect half or more of AUD treatment patients, this recommendation could have far-reaching implications for clinical practice.[6]

As noted in the Introduction, our work builds on and extends two earlier quantitative reviews of this literature. The Tiet and Mausbach review included numerous studies (i.e., 19) that would not have met our stricter inclusion criteria (i.e. we required studies to use randomization and control groups and they did not).[28] The Tiet and Mausbach review, unlike ours, did not include summaries of the effect sizes obtained across studies nor did they integrate outcomes between various internalizing disorder types (i.e., anxiety and depression).[28] Nunes and Levin[29] did restrict their review to randomized controlled trials, however, they did not include studies using psycho-social interventions, nor those in which anxiety disorders were treated. Neither of the past reviews included the subgroup variables “intervention type” and “psychiatric disorder type”, as did we. Therefore, our work extends those reviews and fills gaps in the literature that the past reviews did not.

Alcohol Outcomes

While we did find that treating internalizing symptoms improved alcohol treatment outcomes, the overall summary effect size was small ($\underline{d} = 0.22$). However, examining the four separate domains of alcohol relapse separately shows that measures of quantity, frequency, and intensity of use produced more substantial effects than measures of complete abstinence (quantity $\underline{d} = 0.36$, frequency $\underline{d} = 0.34$, intensity $\underline{d} = 0.31$, and abstinence $\underline{d} = 0.15$) . Consistent with our earlier work, this suggests that supplementing AUD treatment with interventions for internalizing disorders provides more benefit for decreasing the severity of relapse than for completely eliminating alcohol use following treatment.[17]

We also looked at subgroup variables in terms of the impact of internalizing disorder treatment on AUD outcomes. We examined whether studies with larger internalizing effect sizes had a larger impact on alcohol outcomes. In fact, studies with larger internalizing effect sizes do show a statistical trend toward better AUD outcomes (Table 3). However, concluding that better internalizing outcomes mark better AUD treatment outcomes risks making a Type I error since this trend ($p = .09$) did not reach the conventional benchmark statistical significance ($p<.05$).

Internalizing Outcomes

Treatment of internalizing disorders in AUD patients reduced anxiety and depression by approximately one-third of a standard deviation, relative to those receiving AUD treatment plus placebo/control. This modest effect size can be contrasted with the larger effect sizes (ranging from .5 to 1.5) typically produced by the same internalizing treatments applied in psychiatric (vs. AUD) patients.[64–70] It may be that internalizing disorders that co-occur with AUD are more treatment-resistant than those occurring without AUD. Referral patterns or AUD treatment milieus with a conceptualization of chemical dependency as “illness” might also contribute to decreased identification with psychiatric conceptualizations and thus less compliance with psychiatric treatment than in similar treatments delivered outside of the AUD treatment milieu.

Alternatively, internalizing disorders co-occurring with AUDs may differ fundamentally from those that present alone. For example, internalizing disorders that co-occur with AUD might constitute a biologically-based variant that is either less responsive to psychiatric treatment or, conversely, one that is more likely to spontaneously remit without specific treatment. In the former case, absolute change would be suppressed in the treatment condition; in the latter case, absolute change would be enhanced in the placebo (or control) condition. In both cases, effect sizes would be similarly suppressed relative to those obtained in psychiatric treatment trials. In order to investigate this possibility further, we averaged the placebo/control response rate for internalizing disorders from all the studies included in the meta-analysis (34.4%). This rate, however, was comparable to the rate of placebo responding in several psychiatric treatment trials for internalizing disorders; i.e., in the range of 30% to 50%.[71–74] Based on this, we conclude that any suppression of effectiveness of internalizing treatments in AUD vs. psychiatric patients is not due to high levels of spontaneous recovery in the former. Rather, it would appear that suppressed effect sizes for internalizing treatments in AUD treatment patients are due to lower rates of response to the treatment relative to psychiatric patients with no AUD.

The role of subgroup variables might also help to clarify why the effect sizes of internalizing treatments in AUD patients are suppressed relative to those in psychiatric patients. For example, we found that the effect size for CBT treatment on internalizing disorder ($\underline{d}$ =0.66) was closer to the magnitude of effect sizes found in psychiatric samples (see above) than was that for the overall sample. On the other hand, the medication effect size (0.24) was substantially lower than those found in psychiatric patients (again, see above). The disparity found between CBT and medication might indicate that the impact of psychiatric treatment on co-occurring internalizing disorders would have been higher had more of the studies employed CBT (only 3 of 15 studies reviewed used CBT, and only 2 of the 3 reported usable internalizing outcomes). We also explored the data to see whether there were differences in outcomes among various medication types, but found no significant effects differences in medication types.

At this point, we cannot rule out the possibility that the CBT effects, rather than those associated with medication treatment, were anomalous in the studies reviewed. However, the fact that the magnitude of the CBT effect size aligns with what would be expected based on results of CBT trials in psychiatric populations (above) lends support to the idea that the CBT effect size estimate may, in fact, be close to accurate, despite the limited number of studies contributing to the effect size estimate.

Our results also showed that the effect size for internalizing symptoms was larger for anxiety interventions than for depression interventions. Taken at face value, these data suggest that supplementing alcohol treatment as usual with interventions for a co-occurring anxiety disorder may provide more benefit than interventions for co-occurring depression. However, it is not clear why this would be the case. These results could stem from a greater rate of spontaneous recovery from depression as compared to anxiety following AUD treatment, thus lowering the effect size resulting from comparing control to treatment conditions.[6] However, this does not appear to be true in the meta-analysis dataset since the mean control group response rates for depression and anxiety studies did not differ appreciably (33.9% vs. 35.4%, respectively).

Alternatively, it is possible there was some publication bias in the studies included in the meta-analysis with reference to internalizing outcomes. This was suggested by the significance of a publication bias test showing somewhat larger effect sizes in the smaller studies included. It could be that there was greater publication bias among the anxiety studies compared with the depression studies, thus creating an artificial inflation of effect

size for anxiety studies. As noted above, many individual studies did not find significant outcome effects when supplemental internalizing treatment is added to AUD treatment (although their findings integrated by meta-analysis were significant). Therefore, it does not seem likely that negative findings were being suppressed in the published studies. The bias detected was small, so that an estimated pooled effect size that adjusted for the detected difference (i.e., the estimated size of the bias) only marginally reduced the non-adjusted effect size (i.e., $\underline{d} = 0.28$ vs. $\underline{d} = 0.32$). In short, there is nothing in our data to help explain why anxiety was more responsive to treatment than depression.

Limitations

Several methodological issues regarding meta-analysis in general and this meta-analysis in particular should be factored in to the interpretation of our results. The strict restrictions on inclusion required for a meta-analysis are simultaneously a substantial strength and a weakness of the method. Restrictiveness serves as a strength by assuring that the studies included are methodologically rigorous; however, it also serves as a weakness by potentially excluding a large number of studies relevant to a particular topic. In the case of our meta-analysis, over 200 studies were initially identified as potentially relevant to the topic under study but only 15 of these met all of the criteria necessary to be included in the meta-analysis. The possibility that important information was lost by excluding some of these studies should not be ignored.

As noted in the Method section, nine studies identified in the literature search were excluded specifically because they focused on drug use disorders that did not include alcohol. Accordingly, the present findings, because they excluded these studies, cannot be extrapolated to drug abusing populations. Limiting studies to those undergoing AUD treatment (e.g., vs. those in the community or presenting in a psychiatric treatment setting) further limits the generalizability of our findings. Nonetheless, this decision was taken as a strategic reflection of our goal of using the meta-analytic findings to provide treatment recommendations specific to AUD treatment populations.[75] Also, our decision to include studies focused on either depression or anxiety reflected literature showing that these disorders can be reduced to variation on one or two underlying constructs.[31] That is, using the concept of “internalizing disorders” as opposed to separating anxiety and depression is based on the research showing the underlying similarities in these diagnostic entities. However, due to the fact that effect sizes for psychiatric treatment on anxiety were significantly greater than for depression, it may remain important to consider these disorder types separately in this context.

Another potential limitation relates to the fact that, in order to include as many well-qualified studies as possible, we derived our effect sizes from several different measures of alcohol use, depression, and anxiety (see Table 1). There is not a great deal of consistency in the manner in which individual studies report their outcomes, and this inevitable heterogeneity presents a challenge for meta-analysis.[43] We assumed that each of the outcome measures tapped the same underlying construct of relapse, depression, or anxiety and therefore were appropriate to combine. When studies have differing numbers of measures on which an outcome index for meta-analysis is based, it could be expected that there will be less variability in an index based on a study with more measures than one with fewer measures. To minimize this potential problem, as discussed in the Method Section, we followed the lead of past meta-analyses and manuals of meta-analytic strategies.[44,53] Additionally, the statistical program we employed computed a synthetic effect size for studies with multiple outcomes that accounts for the variance introduced with multiple measures by adjusting for the correlation between measures.[53] This allowed us to obtain effect sizes from a greater number of studies, thus adding to our power to conduct a meta-analysis of the studies. Also, we reported the different types of alcohol outcomes

(abstinence, quantity, frequency, and intensity) separately as well as averaged together in attempts to minimize this limitation, as well as listed the measures used to calculate each internalizing effect size (see Table 1).

Conclusions

The preceding discussion opens the way for considering specific clinical recommendations stemming from the findings of this meta-analysis. With small to medium effect sizes overall for internalizing and alcohol outcomes, the question arises whether adding internalizing treatment to alcohol treatment can be justified based on the resources required to apply this approach on a large scale. Because the negative consequences of unsuccessful AUD treatment are potentially great, and because the number of individuals with co-occurring internalizing disorders is known to be large, supplementing alcohol treatment with interventions for co-occurring internalizing disorders could be seen as important, even if the amount of absolute benefit is moderate or even small. Such treatments could be readily incorporated into existing AUD treatment programs where mental health counselors or psychologists already collaborate in treatment of patients seeking treatment for AUD.

This meta-analysis provides the most up to date summary of the literature reviewed. Having 1310 subjects randomized into treatment and control groups in the pool of evaluated studies provides substantial power to estimate stable treatment effects. Even though some of the individual studies included did not reach statistical significance, the meta-analysis method allows the researchers to draw broader conclusions and show significance that might be obscured when looking at individual studies. We reached two broad conclusions based upon the results of this meta-analysis. First, treatments for internalizing disorders that have been validated in psychiatric populations can also effectively treat internalizing disorders in alcohol dependent populations; albeit with somewhat smaller overall effects. Second, supplementing conventional AUD treatment with interventions for co-occurring internalizing disorders provides improvements in alcohol-related outcomes, especially in terms of diminished relapse severity. Therefore, the addition of psychiatric treatment for co-occurring internalizing disorders adds clinically significant value to AUD treatment.

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Table 1

Summary of Descriptive Characteristics and Effect Sizes of Studies

Author and year	Co-Occurring Diagnosis	Treatment Type for Co-Occurring Disorder	# Subjects Random-ized	Measures Used for Internalizing Outcome	Effect Size (d) on Internalizing outcome	Effect Size (d) on Overall Alcohol Outcomes	Effect Size (OR) on Abstinence	Effect Size (d) on Quantity (Q), Frequency (F), Intensity (I)
Bowen et al,[39] (2000)	Panic Disorder	CBT	146	--	--	0.574	A=2.833	--
Brown et al,[38] (1997)	Depression	CBT	35	HAM-D, BDI, POMS-D	0.669	0.380	A=1.800	F=0.598 I= 0.203 Q= 0.397
Cornelius et al,[58] (1997)	Depression	Drug*	51	HAM-D BDI	0.397	0.622	A= 2.057	F= 0.570 Q= 0.720 I= 0.773
Gual et al,[59] (2003)	Depression	Drug*	83	MADRS	0.108	−0.522	A= 0.388	--
Hernandez-Avila et al,[60] (2004)	Depression	Drug†	41	HAM-D	0.357	0.644	--	F= 0.599 Q= 0.460 I= 1.057
Kranzler et al,[61] (1994)	GAD	Drug‡	61	HAM-A	0.442	0.439	--	F= 0.492 Q= 0.413
Kranzler et al,[40] (2006)	Depression	Drug*	328	HAM-D	−0.025	--	--	--
Malcolm et al,[62] (1992)	GAD	Drug‡	67	HAM-A	0.107	0.004	A=0.880	Q= 0.078
McGrath et al,[37] (1996)	Depression	Drug§	69	HAM-D	0.341	0.167	A=2.225	F= 0.085 I= −0.220 Q= 0.090
Moak et al,[36] (2003)	Depression	Drug*	82	BDI, HAM-D	0.211	0.196	--	F= 0.019 Q= 0.374
Randall et al,[22] (2001)	Social phobia	Drug*	15	SPIN	0.826	0.412	--	F= 0.432 I= 0.221 Q= 0.497
Roy[41] (1998)	Depression	Drug*	36	BDI, HAM-D	0.417	--	--	--
Roy-Byrne et al,[63] (2000)	Depression	Drug†	64	HAM-D	0.707	0.160	A=1.498	I= 0.100
Schade et al,[25] (2005)	Social phobia/ Agoraphobia	CBT	96	AQ, ADS, SCL-90	0.702	0.186	A= 1.719	I= 0.129
Tollefson et al,[42] (1992)	GAD	Drug‡	51	HAM-A	0.785	--	--	--

Note. d = Cohen's *d*; OR = odds ratio. ADS = Anxiety Discomfort Scale, AQ = Anxiety Questionnaire; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; GAD = generalized anxiety disorder; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery and Asberg Depression Rating Scale; POMS-D = Profile of Mood States – Depression Scale; SCL-90 = Symptom Checklist; SPIN = Social Phobia Inventory.

[*] Selective Serotonin Reuptake Inhibitor

[†] Serotonin norepinephrine dopamine reuptake inhibitor

[‡] Buspirone

[§] Tricyclic antidepressant

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Table 2

Summary of Pooled Effect Sizes for Internalizing and Alcohol Outcomes (Cohen's d)

Variable	Pooled ES (95% CI)	*p*	*Q*	*p for heterogeneity*	I^2
Internalizing outcome	0.32 (0.17–0.47)	<.001	Q_{13}, 14.18	.36	8%
Overall alcohol use	0.22 (0.02–0.42)	.028	Q_{11}, 15.08;	.18	27%
Abstinence	0.15 (−0.13–0.43)*	.282	Q_7, 10.91	.14	36%
Frequency	0.34 (0.13–0.56)	.002	Q_6, 5.24	.51	0%
Intensity	0.31 (−0.03–0.65)	.072	Q_6, 12.70	.048	53%
Quantity	0.36 (0.16–0.56)	<.001	Q_7, 3.85	.80	0%

* OR 1.32 (0.80–2.18)

Table 3

Subgroup Variable Effects on Internalizing and Alcohol Outcomes

Subgroup Variable	Effect size	*k*	$Q_{between}$	*P*	% Variance explained
Internalizing Outcome					
Treatment type					
CBT	0.66 (0.31–1.02)***	2	4.59	.032	32
Drug	0.24 (0.08–0.40)**	12			
Sample Characteristic					
Anxiety	0.52 (0.27–0.77)***	5	4.05	.044	29
Depression	0.21 (0.03–0.38)*	9			
Overall Alcohol Outcome					
Treatment type					
CBT	0.29 (−0.05–0.64)	3	0.33	.57	2
Drug	0.18 (−0.01–0.37)†	9			
Sample Characteristic					
Anxiety	0.27 (0.004–0.53)*	5	0.33	.57	2
Depression	0.17 (−0.05–0.38)	7			
Internalizing outcome					
< 0.32	0.03 (−0.23–0.28)	4	2.89	.09	20
≥ 0.32	0.32 (0.10–0.54)**	7			

Note. CBT = cognitive behavioral therapy.

† $p = .06$,

* $p < .05$,

** $p < .01$,

*** $p < .001$.